furan (10 ml.) and water (10 ml.). The clear solution was stirred at 0° for a total reaction time of 10 minutes, brought to *p*H 1 with hydrochloric acid and partially evaporated under reduced pressure to remove most of the tetrahydrofuran. An oil separated and rapidly crystallized. The crude product was fractionated as described previously, but only a trace of solid separated from the acetonitrile solution, even on seeding with the dicyclohexylamide. The yield of tosyl-L-pyroglutamic acid cyclohexylamide was 0.47 g. (87%), melting at 184.5–185.5° after softening at 162°. The identity of the substance was confirmed by a mixed m.p. with the authentic compound.

The use of tosyl-L-pyroglutamyl chloride (0.50 g.) in this reaction gave 0.54 g. (89%) of tosyl-L-pyroglutamic acid cyclohexylamide, m.p. 162–163°. A mixture with the authentic material melted at 184.5–185.5°, after softening at 162°. There was only a trace of product insoluble in acetonitrile.

Acknowledgment.—The author wishes to thank Dr. Vincent du Vigneaud for his advice and encouragement during the course of this work. The microanalyses reported herein were carried out by Mr. Joseph Albert.

NEW YORK 21, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE RADIATION LABORATORY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Preparation and Cleavage of Some Codeine Glycols[1]

BY HENRY RAPOPORT, MOHINDRA S. CHADHA AND CALVIN H. LOVELL

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Osmium tetroxide oxidation of codeine and a number of codeine derivatives gave the corresponding 7,8-dihydroxydihydrocodeines, except in the case of codeinone. Yields in this hydroxylation were quite sensitive to the nature of the substituent at carbon 6, and with codeinone dimethyl ketal oxidation of the tertiary amine to a formyl derivative also occurred. Cleavage of the glycols with periodate took place readily, and with those compounds which had no hydrogen at position 6, the cleavage product existed in part as an internal enol hemiacetal. When a hydrogen was present at position 6, introduction of a carbonyl at 7 by periodate oxidation presumably led to an α,β-unsaturated carbonyl compound and oxide ring opening by β-elimination.

As part of a general program directed to the study of morphine and codeine metabolism, we undertook the preparation of a number of codeine glycols both for their interest as possible metabolites and also for their potential use in the synthesis of specifically labeled morphine derivatives. For the latter purpose a method was sought by which ring C could be opened and then reconstituted after replacement of one of the carbons by radioactive carbon.

Ozonolysis is of no avail, since it has been found to attack the aromatic ring A at least as rapidly as the alicyclic double bond in ring C.[2a] Initiation of ring-opening by epoxidation with perbenzoic or monoperphthalic acids also was rejected because these reagents have been shown to form amine oxides first and then to attack the aromatic nucleus as well as the ring C double bond.[2b] This aromatic oxidation apparently is avoidable with performic acid,[3] but the strong acid conditions required were considered unsuitable for some of the contemplated compounds.

An attractive possibility that appeared to have the necessary specificity was oxidation with osmium tetroxide. A series of compounds was chosen all having the Δ^7-double bond and differing only in the substituents at position 6. These were Δ^7-desoxycodeine, codeine, 6-methylcodeine, codeinone dimethyl ketal and codeinone. The hydroxylations were carried out in ether solution at room temperature in the presence of pyridine, and the precipitated osmate esters were cleaved to the corresponding glycols. While the three procedures in the literature for cleaving osmate esters[4–6] gave substantially the same yield, ethanolic sodium sulfite[4] was the method of choice since it gave the most easily purified product.

The results are shown in Table I, and it is interesting to note the strong effect of the 6-substituent on the yield. This is in the expected direction with increasing electronegativity, and codeinone under these conditions, as might be expected, gave no isolable glycol. In those cases, namely, codeinone dimethyl ketal and codeinone, where the yield was poor, only part of the unconverted starting material was recovered, indicating competitive reaction at sites other than the Δ^7-double bond. In the case of codeinone dimethyl ketal, the most thoroughly investigated, oxidation by osmium tetroxide definitely was established to occur alpha to the nitrogen.

From a typical oxidation of codeinone dimethyl ketal with osmium tetroxide, 75% of the starting material was accounted for as glycol IV (11% conversion) and as recovered ketal (64%). The remaining 25% consisted of a number of products only one of which was identified. This was obtained pure by careful chromatography on alumina and was found to contain an additional oxygen (as compared to codeinone dimethyl ketal). That it was not the amine oxide was shown by comparison with an authentic sample of codeinone dimethyl ketal-N-oxide, prepared by oxidation with monoperphthalic acid. Strong absorption in the infrared at 5.98 μ indicated the osmium tetroxide product most likely was an amide, and this was

(1) Supported in part by a grant from the National Institutes of Health, Bethesda, Md.

(2) (a) R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. II, Academic Press, Inc., New York, N. Y., 1952, p. 41; C. H. Lovell, Thesis, Univ. of California, Berkeley, 1955. (b) H. Rapoport and E. C. Galloway, THIS JOURNAL, **77**, 5753 (1955).

(3) M. Gates and G. Tschudi, *ibid.*, **78**, 1380 (1956).

(4) A. Butenandt J. Schmidt-Thomé and H. Paul, *Ber.*, **72**, 1112 (1939).

(5) R. Hirschmann, C. S. Snoddy, Jr., and N. L. Wendler, THIS JOURNAL, **75**, 3252 (1953).

(6) D. H R. Barton, D. A. J. Ives and B. R. Thomas, *J. Chem. Soc.*, 903 (1954).

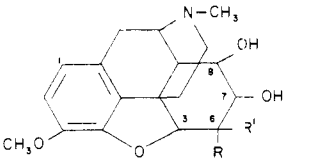


TABLE I

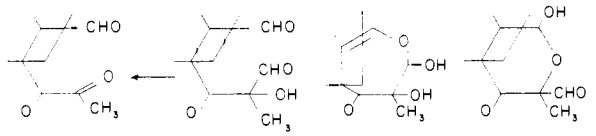
PROPERTIES OF SOME 7,8-DIHYDROXYDIHYDROCODEINE DERIVATIVES

Compound	Yield, %	M.p., °C.	$[\alpha]^{21}D^{a}$	Derivatives	Periodate consumption, *p*H 5–6
I, R = R′ = H	92	248–249	− 18°	Diacetyl, m.p. 122–123° $[\alpha]^{21}D$ −32°[a]	1 mole, rapid
II, R = H, R′ = OH[b]	60	210–211	−123	Triacetyl, m.p. 200–202° $[\alpha]^{21}D$ −79°[a]	1st mole, rapid 2nd mole, very slow
III, R = CH_3, R′ = OH	52	264–265	− 96	O^7,O^8-Diacetyl, m.p. 197–199° $[\alpha]^{25}D$ −102°[c]	1 mole
IV, R = R′ = OCH_3	38	244–245	−102[c]	Diacetyl, m.p. 109–111°	1 mole

[a] Rotations of 1% solutions in 95% ethanol. [b] For previous preparations, see ref. 11. [c] Concn., 0.8.

confirmed by liberation of formic acid on hydrolysis. In addition, this compound absorbed 100 mole % of hydrogen and had a non-basic nitrogen, from which it was concluded to be N-formylnorcodeinone dimethyl ketal. As far as we could determine, this is the first example of oxidation of a tertiary amine to an amide by osmium tetroxide and emphasizes the susceptibility of this position to oxidative attack.[7]

The glycols thus prepared (Table I) then were subjected to the action of periodate. Since it has been observed that tertiary amines consume periodate in alkaline solution,[8] an observation which we have confirmed with a number of codeine derivatives, whereas the ammonium ion forms do not, it was necessary to work in acidic solutions. 6-Methyl-7,8-dihydroxydihydrocodeine (III) consumed one mole of periodate within a few minutes at *p*H 3, 5 and 6, and after this initial uptake there was very little further consumption. Initial cleavage would be expected at the secondary, *cis*-7,8-glycol to give the dialdehyde V, and it had been anticipated that oxidation of V would continue, albeit slower, with consumption of a second mole to give the keto aldehyde VI.

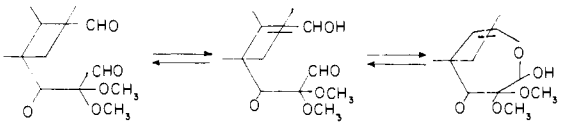


VI V VII VIII

However, lack of any appreciable consumption beyond one mole eliminated this path, and a plausible explanation for the observed behavior was found on detailed examination of the one mole product. The crude product, m.p. 184–185°, obtained in almost quantitative yield, was unchanged on crystallization from methylcyclohexane. Crystallization from water, however, gave an isomeric substance, m.p. 219–220°. That they were not dimorphs was demonstrated by their clearly different absorption in the infrared in chloroform solution. The 184° melting material had a weak band at 2.90 μ and no carbonyl absorption, while the 219° product had a weak band at 2.85 and a strong band at 5.78 μ. Also, the former material gave negative tests with the usual carbonyl-detecting reagents.

This evidence suggests the possibility of VII and VIII (or V) as structures for the low-melting and high-melting isomers, respectively. Of course, if VIII were the predominant form present in the aqueous acid solution, this might also account for the cessation of further oxidation. Alkalization and extraction with ether could lead to the selective removal of the product as VII. Actually, it is not necessary to invoke such a postulate to explain the lack of further oxidation, since the hindered, tertiary nature of the 6-hydroxyl may well be sufficient to block it.

The hypothesis of the oxidation product actually existing as hemi-acetals VII and VIII finds further credibility in similar results found on oxidation of 7,8-dihydroxydihydrocodeinone dimethyl ketal (IV). To avoid ketal hydrolysis, this compound was oxidized with periodate at *p*H 6. Within 1 hr., one mole of periodate was consumed, with practically no further consumption during the next 5 hr. The properties of the resulting product were very sensitive to the *p*H at which extraction was performed. When the reaction mixture was adjusted to *p*H 11 prior to extraction, a product was isolated with m.p. 228–230° and absorption in the infrared (chloroform solution) at 5.78(s), 5.86(s). 6.02(w) and 2.90(w) μ. When isolated by extraction from *p*H 8.5 aqueous solution, the product melted at 96–97°. Its infrared spectrum was quite



IX X XI

different from that of the *p*H 11 product, showing a strong band at 3.0 μ and no absorption in the carbonyl region. Both products had typical morphine-alkaloid ultraviolet absorption spectra.

To explain these results, the *p*H 11 product was assigned structure IX (or a mixture of IX and X), and the *p*H 8.5 product was assigned structure XI. Facile equilibrium between these products was demonstrated by dissolution of either isomer in aqueous acid and isolation of either product, depending on the *p*H (8.5 or 11) at which the extrac-

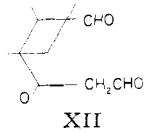
(7) Similar oxidations of >N–CH_3 to >N–CHO have been observed with chromic anhydride in pyridine [T. D. Perrine and L. F. Small, *J. Org. Chem.*, **21**, 111 (1956)] and with manganese dioxide [H. B. Henbest and A. Thomas, *Chemistry & Industry*, 1097 (1956)].

(8) E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley and K. Gerzon, THIS JOURNAL, **76**, 3121 (1954).

tion was conducted. This evidence lends strong support to the concept of the periodate product being a mixture of IX, X and XI, with the nature of the extracted product depending both on the *p*H of the aqueous phase and the various partition coefficients. Thus intramolecular enol-hemiacetal formation seems to occur with considerable facility with the one-mole periodate oxidation products of glycols III and IV. This seven-membered ring formation also may be aided by the disubstitution at carbon 6 in each case.

Oxidation of the glycols from hydroxylation of codeine and Δ^7-desoxycodeine took a more complicated course. 7,8-Dihydroxydihydrocodeine (II) consumed one mole of periodate very rapidly and a second mole much more slowly. However, attempts to isolate either a one-mole or two-mole product all failed to give crystalline material.

With 7,8-dihydroxydihydrodesoxycodeine (I) one mole of periodate was consumed rapidly, and consumption continued at a slower rate to beyond 300 mole %. The one-mole product could not be crystallized, but it had a strong absorption at 5.98 μ and an extinction coefficient of 13,600 at 236 mμ, indicative of an α,β-unsaturated carbonyl group. It gave a strong diazotized sulfanilic acid test, characteristic of morphine alkaloids with a free phenol group at position 4. These observations are compatible with β-elimination from the expected one-mole product XII to give an oxide-ring opened compound. Evidence for such oxide-ring opening



XII

also was found in the oxidation product of glycol II, and elimination of this type may be the predominant reaction when a carbonyl is formed at carbon 7. Of course, in the oxidation products of glycols III and IV, such elimination was prevented by substitution at carbon 6.

Experimental[9]

Preparation of Glycols.—The general procedure for preparing glycols from the Δ^7-codeine derivatives consisted in adding a solution of 10 mmoles of osmium tetroxide and 25 mmoles of purified pyridine in 50 ml. of dry ether to a solution of 10 mmoles of the alkaloid in 50 ml. (or more if required for complete solution) of dry ether. After standing at room temperature for 12 hr., the reaction mixture was centrifuged and the supernatant solution was separated. Two 50-ml. portions of ether were used to wash the precipitated osmate ester, and the combined supernatant solution and washings were examined for unreacted starting material and other by-products.

The osmate ester was hydrolyzed by dissolving a 10-g. portion in 250 ml. of ethanol, adding a solution of 20 g. of sodium sulfite in 100 ml. of water and heating the reaction mixture under reflux on the steam-bath for 4 hr. Filtration then removed precipitated salts which were washed with two 100-ml. portions of hot ethanol, and the combined filtrate and washings were evaporated to dryness *in vacuo*. The residue was treated variously as described below for isolation of the glycols.

(9) All melting points are corrected and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley. Optical rotations were measured on ethanolic solutions in 1-decimeter tubes, unless otherwise specified, and infrared spectra were measured in chloroform.

A. 7,8-Dihydroxydihydrodesoxycodeine (I).—The residue obtained from the hydroxylation of 3.3 g. of Δ^7-desoxycodeine[10] was crystallized from ethanol to give 3.4 g. (92% yield) of 7,8-dihydroxydihydrodesoxycodeine, m.p. 248–249°, $[\alpha]^{21}D$ −18° (*c* 1.0).

Anal. Calcd. for $C_{18}H_{23}O_4N$: C, 68.1; H, 7.3; O, 20.2. Found: C, 68.0; H, 7.4; O, 20.2.

The diacetyl derivative was prepared by heating 1 mmole of the glycol I with 10 ml. of acetic anhydride and 1.5 ml. of pyridine at 80° for 3 hr. Evaporation under reduced pressure, solution of the residue in water and adjustment of the *p*H to 9.5 gave the diacetyl derivative as a precipitate which was crystallized from benzene–heptane, m.p. 122–123°, $[\alpha]^{21}D$ −32° (*c* 0.8).

Anal. Calcd. for $C_{22}H_{27}O_6N$: C, 65.8; H, 6.7. Found: C, 65.9; H, 6.9.

B. 7,8-Dihydroxydihydrocodeine (II).—Codeine (3.5 g.) was hydroxylated by the general procedure, and the residue was distributed between water and ethyl acetate. Continuous extraction with ethyl acetate for 12 hr. and evaporation of the ethyl acetate gave 2.3 g. (60% yield) of material of m.p. 207–209°.[11a] Recrystallization from ethyl acetate–methanol raised the m.p. to 210–211°, $[\alpha]^{21}D$ −123° (*c* 1.0) (reported[11b] m.p. 208–209°).

Anal. Calcd. for $C_{18}H_{23}O_5N$: C, 64.9; H, 6.9; O, 24.0. Found: C, 65.1; H, 7.0; O, 23.6.

The triacetyl derivative was prepared using acetic anhydride and pyridine, as above, and was crystallized from methanol–water, m.p. 200–202°, $[\alpha]^{21}D$ −79° (*c* 1.0) (reported[11b] m.p. 200°).

C. 6-Methyl-7,8-dihydroxydihydrocodeine (III).—Hydroxylation of 2.46 g. of 6-methylcodeine[12] gave a residue which was dissolved in water, and the alkalized aqueous phase was then extracted continuously with ethyl acetate. Concentration of the ethyl acetate and cooling gave 1.41 g. (52% yield) of 6-methyl-7,8-dihydroxydihydrocodeine, m.p. 264–265°, $[\alpha]^{21}D$ −96° (*c* 1.0, 80% ethanol).

Anal. Calcd. for $C_{19}H_{25}O_5N$: C, 65.7; H, 7.3; OCH_3, 8.9. Found: C, 65.6; H, 7.2; OCH_3, 9.0.

The O^7,O^8-diacetyl derivative was prepared as above and was crystallized from benzene–hexane and sublimed, m.p. 197–199°, $[\alpha]^{25}D$ −102° (*c* 0.8).

Anal. Calcd. for $C_{23}H_{29}O_7N$: C, 64.0; H, 6.8. Found: C, 64.0; H, 7.0.

D. 7,8-Dihydroxydihydrocodeinone Dimethyl Ketal (IV).—From 6.7 g. of codeinone dimethyl ketal[13] there was obtained 9.6 g. of osmate ester. The supernatant and washings from this precipitate, on evaporation of the ether, gave 4.7 g. of residue which was examined separately.

The 2.2 g. of residue resulting from decomposition of the osmate ester was chromatographed on 60 g. of alumina. Elution with 100 ml. of chloroform removed 570 mg. of material (fraction A) and chloroform–ethanol (9:1) then removed an additional 870 mg. (fraction B). No further material could be eluted, even with pure ethanol. Fraction A was rechromatographed and with benzene 400 mg. of codeinone dimethyl ketal was recovered. Fraction B was crystallized from ethyl acetate and methanol, and 700 mg. (11% conversion, 38% yield) of 7,8-dihydroxydihydrocodeinone dimethyl ketal was obtained, m.p. 244–245° dec., $[\alpha]^{21}D$ −102 (*c* 0.8).

Anal. Calcd. for $C_{20}H_{27}O_6N$: C, 63.7; H, 7.2; OCH_3, 24.7. Found: C, 63.8; H, 7.1; OCH_3, 24.2.

The diacetyl derivative was prepared by shaking the glycol with acetic anhydride and sodium acetate for 24 hr. at room temperature. Cold aqueous ammonia was then added, the mixture was extracted with chloroform and evaporation of the chloroform gave the diacetyl derivative, m.p. 109–111°.

Anal. Calcd. for $C_{24}H_{31}O_8N$: C, 62.4; H, 6.8. Found: C, 62.4; H, 7.0.

(10) H. Rapoport and R. M. Bonner, THIS JOURNAL, **73**, 2872 (1951).

(11) (a) A similar result has been obtained on osmium tetroxide hydroxylation of codeine by Dr. L. F. Small (personal communication); (b) R. S. Cahn and R. Robinson, *J. Chem. Soc.*, 908 (1926).

(12) S. P. Findlay and L. F. Small, THIS JOURNAL, **72**, 3249 (1950).

(13) H. Rapoport, H. N. Reist and C. H. Lovell, *ibid.*, **78**, 5128 (1956).

The residue (4.7 g.) obtained on evaporation of the supernatant and washings from the osmate ester precipitate was chromatographed on alumina. Benzene eluted 3.9 g. of codeinone dimethyl ketal (total recovery, 4.3 g., 64%), and chloroform eluted a second fraction which was crystallized from benzene and the crystals (m.p. 155–165°) were rechromatographed. They were put on the column with benzene and developed with benzene and then chloroform. Evaporation of the chloroform and crystallization of the residue from benzene–hexane gave 310 mg. of **N-formylnorcodeinone dimethyl ketal**, m.p. 183–184°, $[\alpha]^{21}D$ −206° (*c* 1.0).

Anal. Calcd. for $C_{20}H_{25}O_5N$: C, 66.9; H, 7.0; O, 22.3. Found: C, 66.9; H, 6.6; O, 22.0.

N-Formylnorcodeinone dimethyl ketal had a strong absorption in the infrared at 5.98 μ, it absorbed one mole of hydrogen on hydrogenation with 5% palladized carbon in ethanol, and it showed no basic properties when titrated with perchloric acid in acetic acid. Formic acid was identified as the volatile acid after hydrolysis.[14]

Codeinone Dimethyl Ketal-N-oxide.—Codeinone dimethyl ketal was converted to its N-oxide using the monoperphthalic acid in acetone procedure.[2b] A 75% yield of material was obtained which on crystallization from benzene melted at 191–192°, $[\alpha]^{21}D$ −293° (*c* 0.84). On mixing with the N-formylnorcodeinone dimethyl ketal (m.p. 183–184°), the melting point was depressed 40°.

Anal. Calcd. for $C_{20}H_{25}O_5N$: C, 66.9; H, 7.0. Found: C, 66.6; H, 6.9.

Periodate Cleavage of Glycols.—In each case, the rate of consumption of periodate by the respective glycol was determined at *p*H 5 (acetate buffer) or *p*H 6 (phosphate buffer) and at 25°. The alkaloid concentration was approximately 10^{-3} *M*, the periodate was 4×10^{-3} *M* and the oxidation was followed by withdrawing aliquots and analyzing by standard procedures.[15]

Preparative experiments were similar to the rate determinations, except that the alkaloid concentration was increased two- to sixfold (as solubility permitted), and the periodate was present only in slight excess (*ca.* 20%) over that required for the desired extent of oxidation. After the oxidation had proceeded to the desired point (checked by aliquot analysis), ethylene glycol was added to consume excess periodate, the solution was made alkaline and the alkaloid was extracted with ether or chloroform.

A. Cleavage of 7,8-Dihydroxydihydrodesoxycodeine (I).—In less than 30 min., glycol I had consumed 100 mole % of periodate. A second mole was consumed after 2 hr., and oxidation continued at this slower rate beyond 300 mole %.

From 343 mg. of glycol I, treated with 120 mole % periodate for 1 hr., there was isolated 305 mg. of a brownish oil by adjustment of the *p*H to 8.5, extraction with chloroform and evaporation of the chloroform. This material resisted all attempts at crystallization. It gave a strong phenolic test with diazotized sulfanilic acid, exhibited infrared absorption at 2.74(m), 5.80(w) and 5.98(s) μ, and in the ultraviolet had λ_{max}^{EtOH} 236, ε 13600.

B. Cleavage of 7,8-Dihydroxydihydrocodeine (II).—Within 10 minutes, triol II had consumed 100 mole % of periodate and 14 hr. was necessary for the consumption of a second mole after which consumption ceased.

From larger scale oxidations, stopped after 100 mole % and 200 mole % consumption of periodate, respectively, no crystalline material or derivatives could be obtained. The alkaloidal material, recovered in over 80% yield, showed infrared absorption in the saturated and unsaturated carbonyl regions.

C. Cleavage of 6-Methyl-7,8-dihydroxydihydrocodeine (III).—Oxidations at *p*H 3, 5 and 6 all exhibited 100 mole % consumption of periodate within minutes, and there was very little if any further oxidation.

A 520-mg. sample of the triol III, oxidized by the general procedure above at *p*H 5, gave 390 mg. (75% yield) of the one-mole oxidation product, m.p. 182–183°. After crystallization from benzene–methylcyclohexane, it melted at 184–185°, $[\alpha]^{21}D$ −113° (*c* 1.0).

Anal. Calcd. for $C_{19}H_{23}O_5N$: C, 66.1; H, 6.7; O, 23.2. Found: C, 65.9; H, 6.5; O, 23.4.

With hydroxylamine, phenylhydrazine and 2,4-dinitrophenylhydrazine no derivatives were obtained. The Tollens, Schiff and Fehling tests were negative.

Crystallization from water gave material of m.p. 219–220°, $[\alpha]^{21}D$ −85° (*c* 0.9).

Anal. Calcd. for $C_{19}H_{23}O_5N$: C, 66.1; H, 6.7; O, 23.2. Found: C, 66.3; H, 6.7; O, 23.2.

D. Cleavage of 7,8-Dihydroxydihydrocodeinone Dimethyl Ketal (IV).—Consumption of 100 mole % of periodate by glycol IV required 1 hr. after which no further oxidation occurred.

Preparative oxidations were performed at *p*H 6 and the final extraction of alkaloidal material was made after adjusting the aqueous phase to *p*H 11 or 8.5. Yields of oxidation product in each case were over 80%. The material extracted at *p*H 11 was dissolved in methanol and precipitated with ether. After repeating this procedure, crystalline material, m.p. 228–230°, was obtained. This material could not be recrystallized from a variety of solvents and frequently was very difficult to obtain crystalline.

Anal. Calcd for $C_{20}H_{25}O_6N$ (3 OCH_3): OCH_3, 24.8. Found: OCH_3, 25.0.

Extraction at *p*H 8.5 afforded crude material which on crystallization from benzene–cyclohexane melted at 96–97°, $[\alpha]^{21}D$ −100 (*c* 0.6).

Anal. Calcd. for $C_{20}H_{25}O_6N$: C, 64.0; H, 6.7; O, 25.6. Found: C, 63.8; H, 6.9; O, 25.5.

Either product, dissolved in aqueous acid, and then extracted at the appropriate *p*H, gave the product characteristic of the *p*H of the extraction.

BERKELEY, CALIFORNIA

(14) D. J. Bell, A. Palmer and A. T. Johns, *J. Chem. Soc.*, 1536 (1949).

(15) E. L. Jackson, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 341.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY AND THE DEPARTMENT OF ENTOMOLOGY, UNIVERSITY OF WISCONSIN]

Isolation and Synthesis of an Insect Resistance Factor from Corn Plants

BY EDWARD E. SMISSMAN, JULES B. LAPIDUS AND STANLEY D. BECK

RECEIVED MARCH 2, 1957

The procedure for the isolation of one of three chemical factors which have been shown to be responsible for the resistance of corn plants to attack by the European corn borer is given. The compound was shown to be 6-methoxybenzoxazolinone. The procedure for a chemical synthesis of this resistance factor is reported.

In 1951, Beck[1] proposed the existence, in the corn plant, of a substance which inhibits the growth of the European corn borer. In subsequent work[2–4] it has been shown that the amount of

(1) S. D. Beck, *Proc. North. Cent. Br. Amer. Assn. Econ. Ent.*, **6**, 58 (1951).

(2) S. D. Beck and J. D. Stauffer, *Ann. Ent. Soc. Amer.*, **50**, 166 (1957).

(3) R. S. Loomis, S. D. Beck and J. F. Stauffer, *Plant Physiol.*, in press.

(4) S. D. Beck, *J. Insect Physiology*, in press.