Canescic Acid Lactone.—Canescic acid nitrate (0.256 g.) was dissolved in a solution consisting of pyridine (50 ml.) and acetic anhydride (4 ml.). The solution was heated on the steam-bath for one-half hour. At the end of this time, the initially light yellow solution had turned a deep brown. The solvent was taken off *in vacuo* and the resulting residue was dissolved in chloroform (50 ml.). The chloroform solution was extracted with dilute ammonium hydroxide, dried over anhydrous sodium sulfate and evaporated to dryness under vacuum yielding a mat of fine needles interspersed with tarry globules. This residue was taken up in hot methanol (15 ml.), decolorized with Norite, filtered through Celite and concentrated to approximately 5 ml., whereupon white needles (67 mg.) separated. After recrystallization, the material melted at 333–335°. The infrared spectrum exhibited a band at 2.99 μ (>NH) and a strong band at 5.64 μ characteristic of a γ-lactone. For analysis the sample was dried at 100° (2 mm.) to constant weight.

Anal. Calcd. for $C_{21}H_{24}O_3N_2$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.49; H, 6.95; N, 8.06.

Reconstitution of Canescine.—The amorphous methyl canescate (0.5 g.) was dissolved in dry pyridine (100 ml.) and 3,4,5-trimethoxybenzoyl chloride (2 g.) was added. The mixture was shaken in a stoppered flask for 2.5 hours; at the end of this time, water (2 ml.) was added to decompose the excess acid chloride and the solution was evaporated to dryness *in vacuo*. The residue was taken up in chloroform (50 ml.) and extracted successively with equal volumes of water, dilute sodium hydroxide and water. The chloroform layer was then dried over anhydrous sodium sulfate and taken to dryness *in vacuo*. The resulting amorphous material was dissolved in a minimum of chloroform–benzene (1:3) and was chromatographed as described above for the isolation of naturally occurring canescine. The canescine fraction was recrystallized several times from methanol and recovered by filtration (150 mg.), m.p. 233–234°, $[\alpha]^{24}D$ −135 ± 2° (*c* 1.0 in chloroform). On admixture with a sample of naturally occurring canescine, no melting point depression was observed. The infrared and ultraviolet spectra were identical. For analysis the sample was dried to constant weight at 100° (2 mm.).

Anal. Calcd. for $C_{32}H_{38}O_8N_2$: C, 66.43; H, 6.62; N, 4.84; 5 $-OCH_3$, 26.81. Found: C, 66.44; H, 6.56; N, 4.81; $-OCH_3$, 26.52.

ADDED IN PROOF.—Since the submission of this paper several communications have appeared in the literature in which the isolation and structure of this alkaloid also is reported; *cf.* E. Schlittler, P. R. Ulshafer, Mary L. Pandow, Regina M. Hunt and L. Dorfman, *Experientia*, 11, 64 (1955); H. B. MacPhillamy, L. Dorfman, C. F. Huebner, E. Schlittler and A. F. St. Andre, THIS JOURNAL, **77**, 1072 (1955); A. Stoll and A. Hofmann, *ibid.*, **77**, 821 (1955).

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Rauwolfia Alkaloids. III.[1] Recanescine, a New Sedative Principle of *Rauwolfia canescens* Linn.

BY NORBERT NEUSS, HAROLD E. BOAZ AND JAMES W. FORBES

RECEIVED FEBRUARY 12, 1955

Recanescine, a new sedative principle of *Rauwolfia canescens* Linn. has been isolated. Hydrolysis of recanescine yielded 3,4,5-trimethoxybenzoic acid and methyl recanescate, characterized as a tosyl ester. Reductive cleavage of recanescine afforded recanescic alcohol and 3,4,5-trimethoxybenzyl alcohol. From the spectral data, the structure of recanescine as 11-desmethoxyreserpine has been suggested.

Rauwolfia canescens Linn., a species of the family of *Apocyanaceae*, is closely related to *Rauwolfia serpentina* Benth. On occasion it has been found in the commercial lots of the latter as an adulterant. The pharmacognosy of the plant has been studied recently by Youngken.[2] The alkaloidal content of the plant was investigated first by Chatterjee[3] and others[4] leading to isolation of rauwolscine, reserpine, serpentine and yohimbine.

We should like to report now the isolation and characterization of a new sedative principle of this plant. This new alkaloid for which we propose the name recanescine is a weak base and very closely related to reserpine. Recanescine was isolated by chromatography of the mother liquor from crystallization of reserpine on acid-washed alumina using benzene as eluent. On paper chromatography it had a higher R_f value (*ca.* 0.65) than reserpine (*ca.* 0.4) in xylene–formamide system using formamide pretreated paper. The alkaloid crystallized from ethyl acetate with one mole of the solvent and melted at 220–222° dec. The material crystallized from methanol, melted first at 150°, then resolidified and melted at 228–230° dec. Interestingly, the X-ray powder diffraction pattern of this compound was identical with that of reserpine (also crystallized from methanol); however, their indices of refraction were different.

The analysis of the ethyl acetate solvate gave satisfactory results for a $C_{32}H_{38}O_8N_2$ compound with one mole of ethyl acetate. Preparation of a hydrochloride and its analysis substantiated the empirical formula of recanescine. The molecular weight determination from X-ray data was also in excellent agreement with the above formulation.

Ultraviolet spectrum of recanescine in methanol showed the following bands: λ_{max} 216 mμ (log ϵ 4.78), λ_{max} 271 mμ (log ϵ 4.25) and λ_{max} 289 mμ (log ϵ 4.06). A summation of the ultraviolet absorption spectrum of yohimbine and 3,4,5-trimethoxybenzoate in a mole per mole ratio resulted in a spectrum remarkably similar to that of recanescine. The computed spectrum possessed three maxima: λ_{max} 216 mμ (log ϵ 4.76), λ_{max} 268 mμ (log ϵ 4.20) and λ_{max} 289 mμ (log ϵ 4.01). These data indicate that the ultraviolet chromophores in recanescine consist of 2,3-disubstituted indole and 3,4,5-trimethoxybenzoate.

This formulation was confirmed by the data obtained from the degradation products of recanescine using reductive cleavage with lithium aluminum hydride in tetrahydrofuran. One product of

(1) Rauwolfia Alkaloids. II. N. Neuss, *et al.*, THIS JOURNAL, **76**, 3234 (1954).

(2) Heber W. Youngken, Sr., *J. Am. Pharm. Assoc.*, **43**, 70 (1954).

(3) A. Chatterjee, *Naturwissenschaften*, **40**, 215 (1954), and references cited therein.

(4) M. W. Klohs, *et al.*, THIS JOURNAL, **76**, 1381 (1954); E. Haack, *et al.*, *Naturwissenschaften*, **41**, 479 (1954).

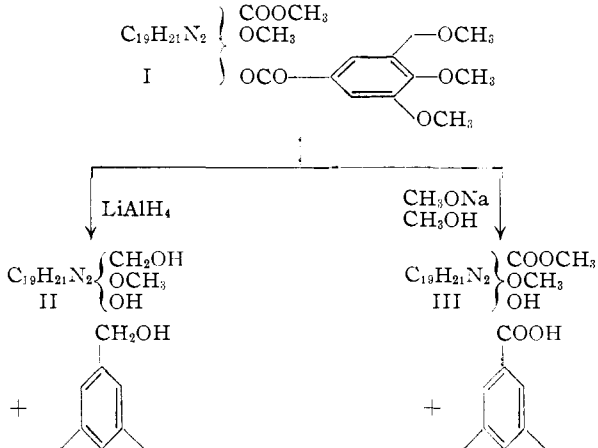
this reaction was found to be 3,4,5-trimethoxybenzyl alcohol identified as the *p*-nitrobenzoate.[5] The other product was an amino alcohol which we called recanescic alcohol. Recanescic alcohol had a typical ultraviolet spectrum of a 2,3-disubstituted indole: λ_{max} 225 mμ (log ϵ 4.51), λ_{max} 282 mμ (log ϵ 3.86) and λ_{max} 290 mμ (log ϵ 3.78).

Mild hydrolysis of recanescine using sodium methoxide in methanol[6] also yielded two products. One was identified readily as 3,4,5-trimethoxybenzoic acid. The other could not be crystallized but was characterized as a tosyl ester. In analogy to the nomenclature used in the chemistry of reserpine,[6] we would like to use the trivial name of methyl recanescate for this fragment.

Methyl recanescate O-tosylate had a typical ultraviolet absorption of a 2,3-disubstituted indole (*e.g.*, recanescic alcohol) at the longer wave length. The additional absorption at shorter wave length is accounted for by the presence of the O-tosyl grouping in this molecule: λ_{max} 224 mμ (log ϵ 4.64), λ_{max} 280 mμ (log ϵ 3.86) and λ_{max} 291 mμ (log ϵ 3.79).

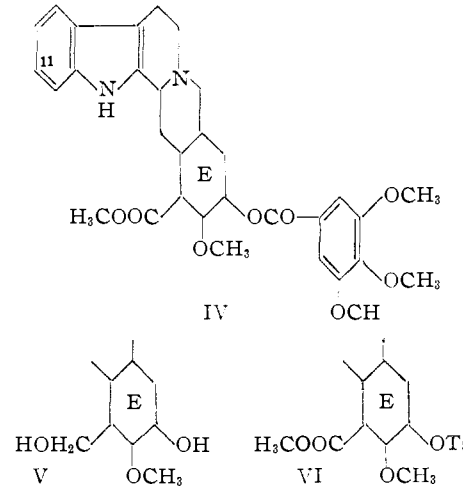
The infrared spectrum of this derivative in chloroform solution was essentially that of the tosyl ester of methyl reserpate without the bands characteristic of 2,3-disubstituted-6-methoxyindole.

The analytical data result in these partial structures for recanescine (I), recanescic alcohol (II) and methyl recanescate (III).



The $C_{19}H_{21}N_2$ ring system of recanescine could not be elucidated from the dehydrogenation studies in view of the small amount of recanescine available for this study. However, using the same technique of infrared analysis which led to the derivation of the structure of reserpinine,[1] we were able to deduce the nature of the $C_{19}H_{21}N_2$ nucleus of recanescine. The infrared spectrum of recanescine in chloroform solution differs from that of reserpine in the obvious absence of the band at 6.13 μ and easily detectable proportional decrease in intensity of bands at 6.33, 6.67, 8.62 and 9.70 μ. These five bands were shown to be characteristic of 2,3-dimethyl-6-methoxyindole[5] and also were present at nearly the same wave lengths in a non-substituted 6-methoxyindole. All the differences between the spectrum of reserpine and recanescine arise from the absence of the methoxyl at C_{11} in the latter. This formulation was demonstrated easily by the summation spectrum of recanescine and 2,3-dimethyl-6-methoxyindole at equimolar concentration in chloroform solution (Fig. 2). This spectrum was practically identical with that of reserpine.

Our data clearly indicate that recanescine is 11-desmethoxyreserpine (IV). Accordingly, recanescic alcohol is represented by V and methyl recanescate O-tosylate by VI.



Recanescine was shown to have the same pharmacological properties as reserpine in monkeys and rabbits (sedation, myosis and ptosis) and anesthetized cats and dogs (blood pressure lowering, apparent enhancement of the pressor response to epinephrine and inhibition of blood pressure response to bilateral carotic occlusion).[7]

The pharmacological results indicate that the presence of methoxyl at C_{11} is not necessary to produce physiological effects typical of reserpine.

We are attempting to establish the stereochemistry of recanescine by converting it to a known derivative of the yohimbine series.

ADDED IN PROOF.—Since submission of this manuscript, Stoll and Hofmann[8] have reported isolation of pseudoyohimbine and canescine from the root of *Rauwolfia canescens*. The latter compound is probably identical with recanescine. In another paper Stoll, *et al.*,[9] described isolation of reserpiline, isoreserpinine, isoreserpiline and aricine from the leaves of the same species. We have since isolated small amounts of aricine from the root of the plant. Schlittler and co-workers[10] have also reported isolation of 11-desmethoxyreserpine which they called deserpidine. A sample of this alkaloid, kindly supplied by Dr. Schlittler and crystallized from ethyl acetate, was identical with our recanescine. Finally MacPhillamy, *et al.*,[11] have assigned to the new alkaloid as well as to reserpine the 3-epi-allo-yohimbane skeleton.

Acknowledgment.—We gratefully acknowledge invaluable assistance by the following: Dr. H. A. Rose, X-ray data; Dr. E. W. Grant, paper chro-

(5) Norbert Neuss, *et al.*, THIS JOURNAL, **76**, 2463 (1954).

(6) This procedure was first used in the structure elucidation of reserpine by L. Dorfman, *et al.*, *Helv. Chim. Acta*, **37**, 59 (1954).

(7) I. H. Slater, R. C. Rathbun, F. G. Henderson and N. Neuss, *Proc. Soc. Exp. Biol. Med.*, **88**, 293 (1955).

(8) A. Stoll and A. Hofmann, THIS JOURNAL, **77**, 821 (1955).

(9) A. Stoll, *et al.*, *Helv. Chim. Acta*, **38**, 270 (1955).

(10) E. Schlittler, *et al.*, *Experientia*, **11**, 64 (1955).

(11) H. B. MacPhillamy, *et al.*, THIS JOURNAL, **77**, 1071 (1955).

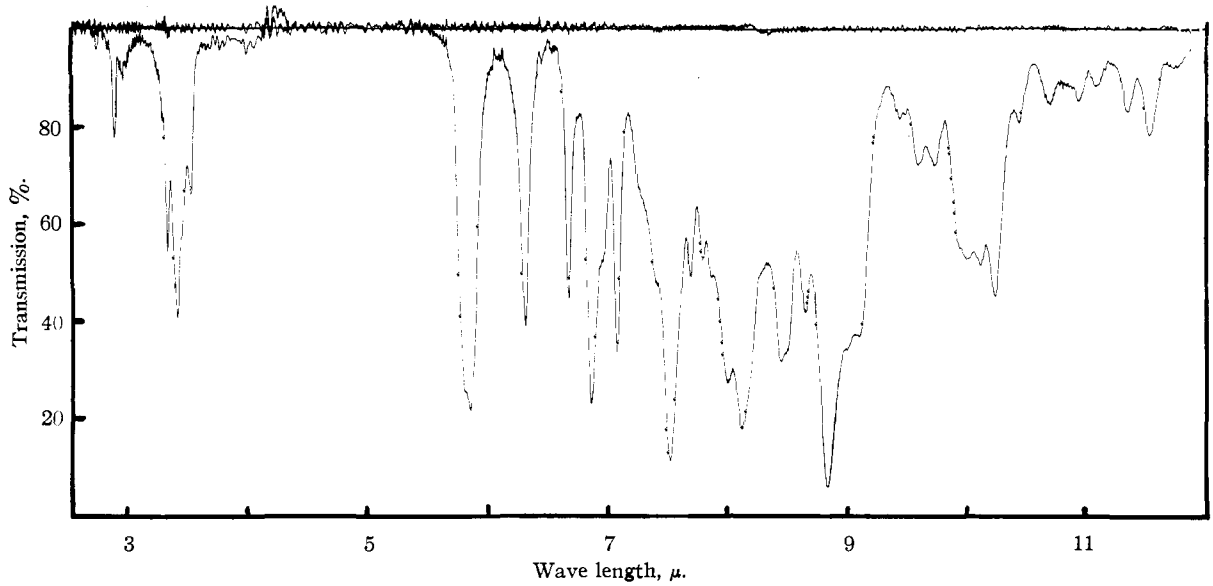


Fig. 1.—Infrared spectrum of recanescine in $CHCl_3$ at 0.13 *M* in 0.10 mm. path.

matography; Messrs. W. L. Brown, G. M. Maciak and Miss G. M. Beckmann, elementary analyses and group determination; Miss M. Hofmann, ultraviolet spectra; Mrs. H. M. Arndt and Mr. T. V. Parke, infrared spectra; Miss M. Livezey, technical assistance. We would like to thank Dr. G. H. Svoboda for mother liquors from crystallization of reserpine, isolated from *R. canescens*.

Experimental[12]

Isolation and Characterization of Recanescine.—A solution of 7.4 g. of residue (obtained by concentration of methanolic mother liquor from crystallization of reserpine) in 50 ml. of benzene was chromatographed on a column of acid-washed (300 g.) alumina (Merck). Fractions of 100 ml. were collected and evaporated under reduced pressure. The first fourteen fractions were combined and crystallized from ethyl acetate yielding 1.4 g. of recanescine. One more recrystallization afforded long colorless prisms, m.p. 220–222° dec., $[\alpha]^{26}D$ −118° (*c* 1.01 in $CHCl_3$). For analysis the sample was dried at room temperature (0.05 mm.) for 1 hour.

Anal. Calcd. for $C_{32}H_{38}O_8N_2CH_3COOC_2H_5$: C, 64.85; H, 6.95; N, 4.20; OCH_3 (5) and OC_2H_5 (1), 8.386 mg. of AgI; CH_3CO (1), 6.46; mol. wt., 666.8. Found: C, 64.51, 65.22, 64.71; H, 6.95, 6.92, 6.92; N, 4.17; OCH_3 (5) and OC_2H_5 (1), 8.311 mg. of AgI; CH_3CO (1), 6.50; mol. wt. (X-ray data), 669.3.

For infrared spectrum see Fig. 1. The spectrum was recorded on a sample free of ethyl acetate of crystallization.

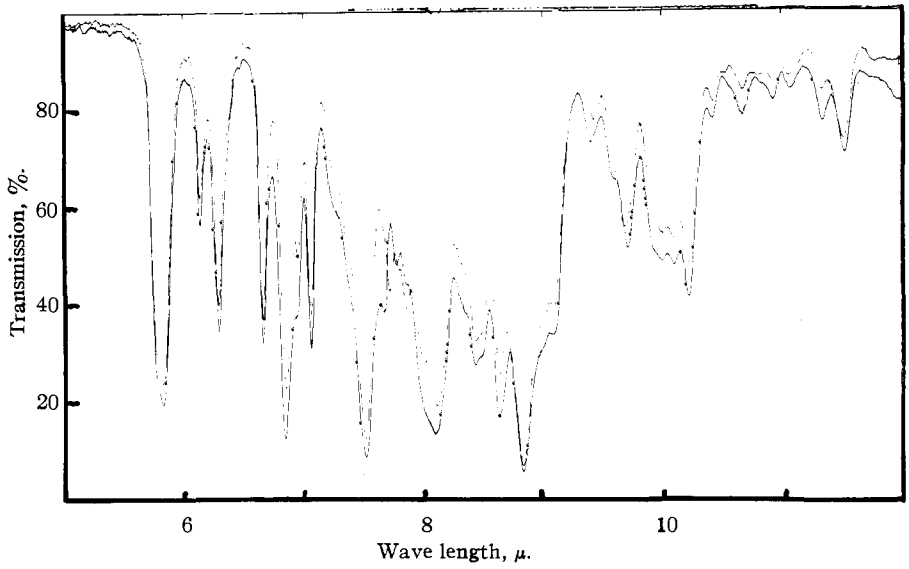


Fig. 2.—Infrared spectra of reserpine and an equimolar solution of 2,3-dimethyl-6-methoxyindole and recanescine. The solid line spectrum is reserpine at 0.13 *M* in $CHCl_3$ in 0.10 mm. path. The spectrum distinguished by dotted portions is an equimolar solution of mentioned models at 0.12 *M* in $CHCl_3$ in 0.10 mm. path.

Recanescine Hydrochloride.—The salt was prepared by the usual procedure and recrystallized from methanol–ether. The analytical sample was dried 1 hour at room temperature and contained one mole of methanol of crystallization, m.p. 241–243° dec.

Anal. Calcd. for $C_{32}H_{38}O_8N_2 \cdot HCl \cdot CH_3OH$: C, 61.24; H, 6.70; N, 4.33; Cl, 5.48. Found: C, 60.96; H, 6.57; N, 4.51; Cl, 5.65.

Reductive Cleavage of Recanescine; Isolation of Recanescic Alcohol and 3,4,5-Trimethoxybenzyl Alcohol.—To a stirred suspension of 200 mg. of lithium aluminum hydride in dry tetrahydrofuran was added dropwise a solution of 300 mg. of recanescine (free of solvent of crystallization) in 20 ml. of dry tetrahydrofuran. The mixture was boiled under reflux for 4 hours, then cooled and decomposed with 6 ml. of water. After heating under reflux for 1 hour, inorganic salts were removed by filtration. The filtrate was freed from solvent under reduced pressure at 30° and the residue crystallized upon addition of ethanol. The crude recanescic alcohol weighed 110 mg. The material was recrystallized

(12) All melting points are uncorrected and were taken on a Fisher–Johns melting point apparatus. The substances were inserted at 150° unless otherwise mentioned.

once more from dilute alcohol and formed long prisms, m.p. 214–215° dec. It was dried for analysis 4 hours at 80° (0.05 mm.).

Anal. Calcd. for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.51; H, 8.00; N, 7.78.

The mother liquor from the first crystallization of recanescic alcohol was evaporated under reduced pressure and a small amount of an oily residue (*ca.* 40 mg.) obtained. This was treated in the usual manner with *p*-nitrobenzoyl chloride in pyridine. The derivative (*ca.* 15 mg.) was identical with material prepared from an authentic sample of 3,4,5-trimethoxybenzoyl alcohol[5] (m.p., mixed m.p. and X-ray patterns).

Partial Hydrolysis of Recanescine; Isolation of Methyl Recanescate *O*-Tosylate and 3,4,5-Trimethoxybenzoic Acid.—To a solution of 100 mg. of sodium in 25 ml. of absolute methanol was added 670 mg. of recanescine (free of solvent of crystallization). After boiling for 1 hour under reflux and concentration to 5 ml. *in vacuo*, the reaction mixture was acidified and extracted exhaustively with ether. The ethereal solution was evaporated to dryness, the residue dissolved in hot sodium hydroxide solution (*ca.* 10%), filtered and acidified. Beautiful prisms of 3,4,5-trimethoxybenzoic acid, m.p. 168°, slowly separated. This material was identical with the authentic sample of the acid (m.p., mixed m.p. and X-ray patterns).

The aqueous phase from ether extraction was made basic and extracted with chloroform, dried over anhydrous sodium sulfate and evaporated to dryness. The residue (400 mg.) was dissolved in 5 ml. of dry pyridine, 800 mg. of recrystallized, dry tosyl chloride added, and allowed to stand for three days at room temperature. After the usual work-up, the crude tosyl ester was recrystallized from boiling benzene with addition of charcoal. The yield was 215 mg. of material, m.p. 210–211° dec. It was recrystallized twice from the same solvent and dried for 4 hours at 100° (0.05 mm.) for analysis.

Anal. Calcd. for $C_{29}H_{34}O_6N_2S$: C, 64.66; H, 6.36; N, 5.20; S, 5.95. Found: C, 64.84; H, 6.50; N, 5.15; S, 5.88.

INDIANAPOLIS 6, INDIANA

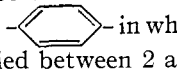
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Macro Rings. XI. Reactions in the 1,4-Decamethylenebenzene Series[1]

BY DONALD J. CRAM AND MARTIN CORDON

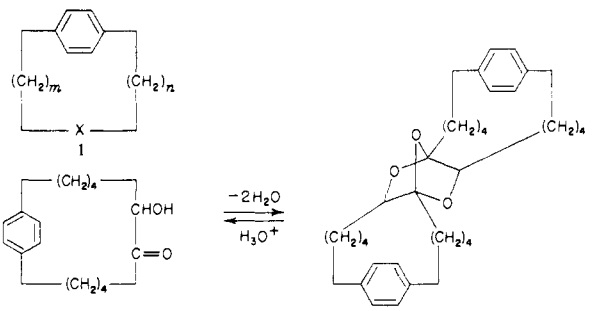
RECEIVED JANUARY 21, 1955

Syntheses, reactions and physical properties are described for compound I ($n = m = 4$) with X = —C≡C—, —C=CH— (*cis*), —CH_2CHOH— (both enantiomers) and for I ($m = 4$, $n = 3$) with X = O=C—CH=CH—.

Previous papers[2] in this series have reported the preparation of I ($m = n = 4$) with X = CH_2CH_2, CHOHCO, CHOHCHOH, COCO (and its enol) and CH_2CO, as well as various derivatives of these substances. Of these compounds, only I ($m = 4$, $n = 3$) where X = CH=COHCO and its acetate possess ultraviolet spectral properties which cannot be predicted by simple addition of the aromatic and X chromophores. Other papers[3] have recorded the preparation of I with –X– = –  – in which m and n were systematically varied between 2 and 6. In this series, abnormal ultraviolet spectral properties were observed for those compounds in which n or $m < 4$, the spectra of the higher homologs being normal as compared to open chain models.

The objectives of this investigation were (1) to prepare and study the properties of I with $m = n = 4$ and X = C≡C or CH=CH (*cis*), and of I with $m = 3$, $n = 4$ and X = CH=CHCO; and (2) to prepare and resolve I ($m = n = 4$) with X = CH_2CHOH. This latter objective is a preliminary to solvolysis studies designed to determine if the π-electrons of the benzene become involved in ionization processes in the side chain.

Preparation of Derivatives of 1,4-Decamethylenebenzene.—Acyloin II[2a] (the parent cyclic starting material) was found upon standing to undergo self-condensation to give material which upon treatment with acetic anhydride gave a substance whose properties are consistent with the bicyclic bis-ketal structure, III. The analysis and molecular weight of the compound indicated it to be



a dimer of the acyloin minus one mole of water. The infrared spectrum of the substance was devoid of bands in the hydroxyl or carbonyl regions, but possessed a strong band at 9.30 μ characteristic of ether linkages. The compound reacted very slowly with a solution of 2,4-dinitrophenylhydrazine in dilute acid, and with bismuth oxide in acetic acid.[4] Although a number of stereoisomeric forms of III are possible, no detailed structural assignment is possible. This bicyclic ketal probably arose by the action of the acetic anhydride on the simple dimer containing the cyclic hemiketal linkage IV, which function has been observed to arise from other acyloins.[5]

The acyloin II was oxidized (Bi_2O_3) to a mixture of α-diketone and enol[2a] which was heated with

(1) This work was generously supported by a grant from the Upjohn Company.

(2) (a) D. J. Cram and H. U. Daeniker, THIS JOURNAL, **76**, 2743 (1954); (b) D. J. Cram and M. Cordon, *ibid.*, **77**, 1810 (1955).

(3) (a) D. J. Cram and H. Steinberg, *ibid.*, **73**, 5691 (1951); (b) H. Steinberg and D. J. Cram, *ibid.*, **74**, 5388 (1952); (c) D. J. Cram and N. L. Allinger, *ibid.*, **76**, 726 (1954); (d) N. L. Allinger and D. J. Cram, *ibid.*, **76**, 2362 (1954); (e) J. Abell and D. J. Cram, *ibid.*, **76**, 4406 (1954); (f) D. J. Cram and N. L. Allinger, *ibid.*, **76**, 6132 (1954).

(4) W. Rigby, *J. Chem. Soc.*, 793 (1951).

(5) J. C. Sheehan, R. C. O'Neill and M. H. White, THIS JOURNAL, **72**, 3376 (1950).