[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, PRINCETON, N. J., AND THE NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS, URBANA, ILL.]

The Synthesis of Some Model Compounds Related to Tetrahydrocannabinol

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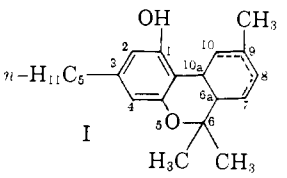
RECEIVED MARCH 5, 1960

The structures of the tetrahydrocannabinols, the active constituents from the *Cannabis* resins responsible for the physiological activity of marijuana, have not yet been established with certainty, either by degradation or by synthesis. We have examined possible stereospecific synthetic routes in a model series. A Diels–Alder reaction between isoprene and 3-carbethoxycoumarin yielded 6a-carbethoxy-9-methyl-6a,7,10,10a-tetrahydro-6-dibenzopyrone (VI), whose structure was confirmed by dehydrogenation, with simultaneous loss of the carbethoxy group, to 9-methyl-6-dibenzopyrone (VII). The structure of VII in turn was established by degradation to 2,5-dimethyl-2′-hydroxybiphenyl (IX), which was synthesized independently. Careful hydrolysis of VI yielded both the *cis* and *trans* isomers of 9-methyl-6a,7,10,10a-tetrahydro-6-dibenzopyrone (XVII and XVIII) which were separated and characterized. Treatment of each of these lactones with methylmagnesium iodide followed by cyclization of the resulting *t*-carbinols with *p*-toluenesulfonic acid in xylene yielded *cis*- and *trans*-6,6,9-trimethyl-6a,7,10,10a-tetrahydrodibenzopyran (XXI and XXII), two of the desired tetrahydrocannabinol models. From an inspection of the ultraviolet absorption spectra of these products, it appeared that XXI was contaminated with isomeric material probably resulting from double bond migration.

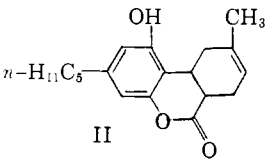
As a result of the extensive investigations of Adams[3] and Todd,[4] the structure of the tetrahydrocannabinols, the active constituents of the oil from the *Cannabis* resins responsible for the physiological activity of marijuana, has been established with certainty to be I, with the exception that the configuration of the two asymmetric carbon atoms at positions 6a and 10a, and the position of the



I

alicyclic double bond, are not known. These questions remain open in spite of numerous attempts to prepare individual isomers by synthesis. For example, the most direct approach to the synthesis of a tetrahydrocannabinol isomer with a *trans* ring fusion and an 8–9 double bond would involve the Diels–Alder reaction of *o,o′*-dihydroxy-*p*-(*n*-amyl)-cinnamic acid with isoprene,[5] but this approach could not be used because of the inactivity of *o,o′*-dihydroxycinnamic acid in the Diels–Alder reaction.[6] With the hydroxyl groups blocked by methylation, the Diels–Alder reaction was successful, but subsequent demethylation failed.[7] By an extension of this reaction sequence, however, a synthetic tetrahydrocannabinol with a (presumably) non-conjugated double bond was prepared in low yield. Although the ring junction is undoubtedly *trans* in this synthetic material, the position of the isolated double bond cannot be considered certain because of the severity of the acidic demethylating conditions employed.[7]

An attractive route to tetrahydrocannabinol which was considered by Adams[8] involved the Diels–Alder reaction of isoprene with an appropriately substituted coumarin, which would have given in one step the requisite tricyclic lactone intermediate II. This pathway could not be exploited, however, because model experiments showed that even coumarin itself was too unreactive to give an adduct with isoprene.



II

We wish to report in this paper the successful use in the Diels–Alder reaction with isoprene of two coumarins substituted in the 3-position with electronegative groups, and the conversion of one of the resulting products into both the *cis* and *trans* isomers of 6,6,9-trimethyl-6a,7,10,10a-tetrahydrodibenzopyran (XXI and XXII) as models for two of the possible isomers of tetrahydrocannabinol.

It is well known that introduction of electronegative groups in conjugation with an olefinic double bond increases its dienophilic activity in the Diels–Alder reaction.[9] It was to be expected, therefore, that the introduction of electronegative groups in the 3- or 4-positions of coumarin would be reflected in an enhancement of its activity in the Diels–Alder reaction. We have found that both 3-cyanocoumarin (III) and 3-carbethoxycoumarin (IV) react satisfactorily with isoprene under moderate conditions to give the crystalline adducts V and VI, respectively. Only one of the two possible structural isomers was isolated in each case, and in each product the methyl group was shown to be in the desired 9-position. Thus, dehydrogenation of V and VI over palladium-on-carbon, with concomitant loss of the nitrile and carbethoxy groups respectively, yielded the same product, 9-methyl-6-dibenzopyrone (VII). The structure of VII was then determined by reduction with lithium aluminum hydride to an intermediate diol VIII which upon catalytic hydrogenation was converted to 2,5-dimethyl-2′-hydroxybiphenyl (IX). An in-

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(2) Parke–Davis and Co. Fellow, 1952–1954.

(3) R. Adams, C. K. Cain, W. P. McPhee and R. B. Wearn, THIS JOURNAL, **63**, 2209 (1941), and previous papers in this series.

(4) F. Bergel, A. L. Morrison, H. Rinderknecht, A. R. Todd, A. D. MacDonald and G. Woolfe, *J. Chem. Soc.*, 286 (1943), and previous papers in this series.

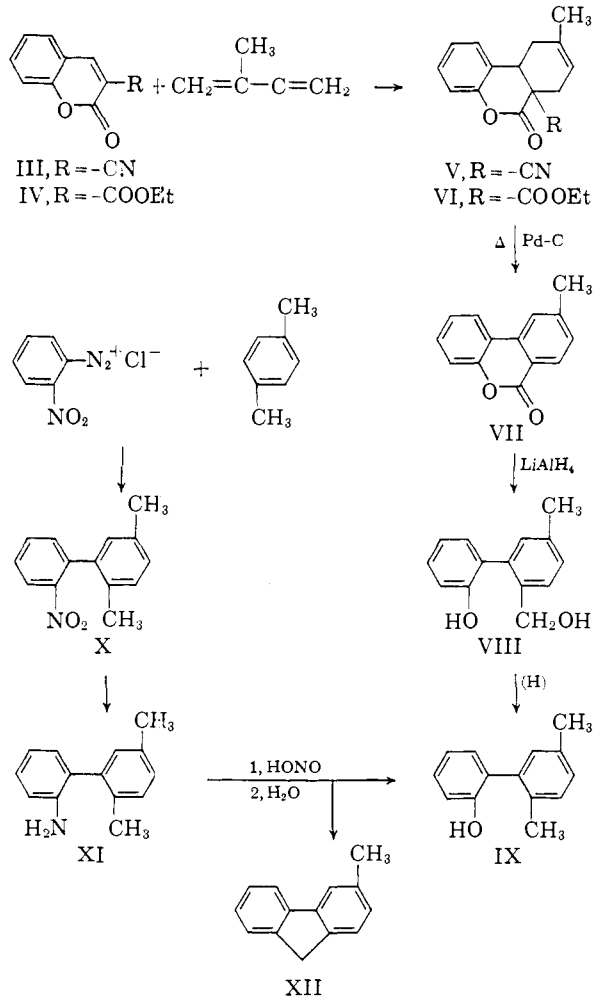
(5) R. Adams and R. B. Carlin, THIS JOURNAL, **65**, 360 (1943).

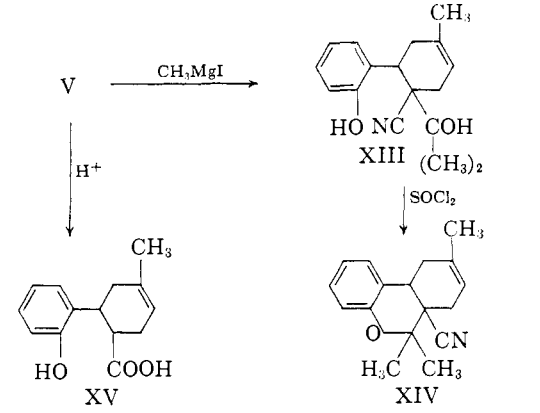
(6) R. Adams and T. E. Bockstahler, *ibid.*, **74**, 5346 (1952).

(7) Z. W. Wicks, Ph.D. Thesis, University of Illinois, 1944.

(8) R. Adams, W. D. McPhee, R. B. Carlin and Z. W. Wicks, THIS JOURNAL, **65**, 356 (1943).

(9) For a recent example, see W. J. Middleton, R. E. Heckert, E. L. Little and C. G. Krespan, *ibid.*, **80**, 2783 (1958).





dependent synthesis of IX then confirmed its structure. A Gomberg coupling of *o*-nitrobenzenediazonium chloride with *p*-xylene gave 2,5-dimethyl-2′-nitrobiphenyl (X), which upon catalytic reduction to XI followed by diazotization and hydrolysis yielded a mixture of 3-methylfluorene[10] and 2,5-dimethyl-2′-hydroxybiphenyl (IX). This latter compound was identical with the product obtained by degradation of V and VI.

Treatment of 9-methyl-6a-cyano-6a,7,10,10a-tetrahydro - 6 - dibenzopyrone (V) with excess methylmagnesium iodide at room temperature yielded a crystalline diol XIII which was cyclized to 6a-cyano-6,6,9-trimethyl-6a,7,10,10a-tetrahydrodibenzopyran (XIV) either with formic acid or with thionyl chloride. However, all attempts to remove the cyano group from XIV met with failure. For example, treatment of XIV with a mixture of sulfuric and acetic acid at 100° for 59 hours, 50% sulfuric acid at 140° for 2 hours, hot polyphosphoric acid or alkaline hydrogen peroxide were equally ineffective. From all of these hydrolysis attempts a crystalline material was isolated which proved to be isomeric with XIV. Examination of its infrared spectrum revealed the presence of a cyano group and the absence of hydroxyl or carbonyl groups, and it seems probable that isomerization of the alicyclic double bond or perhaps of the 6a,10a-*cis* ring fusion had taken place.

Direct hydrolysis of the Diels–Alder adduct V yielded 4-methyl-6-(*o*-hydroxyphenyl) - Δ^3 - tetrahydrobenzoic acid (XV) in very low yield, but its stereochemistry must be considered in doubt because of the probable symmetrical dicarboxylic acid intermediate in the hydrolysis. Possible routes to the desired tetrahydrocannabinol model compounds utilizing V were then abandoned in favor of procedures involving 6a-carbethoxy-9-methyl - 6a,7,10,10a - tetrahydro - 6 - dibenzopyrone (VI), the Diels–Alder adduct from isoprene and 3-carbethoxycoumarin.

Initial attempts to utilize VI in a reaction sequence analogous to the one described above with V were unsuccessful. Thus, treatment with excess methyl magnesium iodide yielded a product which resisted purification, and attempted hydrolysis of the crude material failed to give an organic acid. However, careful hydrolysis of VI itself yielded an unstable dicarboxylic acid XVI which underwent decarboxylation and subsequent lactonization by heating in xylene to give a mixture of two isomeric lactones in approximately equal amounts. The lower melting isomer (m.p. 96–97°) is assigned the structure *cis*-9-methyl-6a,7,10,10a - tetrahydro - 6-dibenzopyrone (XVII), and the higher melting isomer (m.p. 143–144°) the corresponding *trans* configuration (XVIII) on the basis of the following arguments: (1) Adams and Bockstahler[6] have described the formation of a lactone, m.p. 140–140.5, in low yield from the reaction of methyl *trans*-*o*-hydroxycinnamate with isoprene; it seems probable that this is the *trans* isomer XVIII. (2) Inspection of molecular models shows that the *cis* isomer is rather crowded, with the cyclohexene ring almost at right angles to the benzene ring, while the *trans* isomer is less crowded and roughly planar. One would thus predict *cis* to *trans* isomerization to take place under appropriate conditions. In accordance with these predictions, the lower melting isomer is readily converted to the higher melting isomer upon heating in the presence of ammonium acetate. (3) Addition of hydrogen bromide to the lower melting isomer yielded a single adduct in 81% yield, while addition of hydrogen bromide to the higher melting isomer gave a mixture of products from which a pure adduct could be obtained only after repeated fractional crystallization. These results are in agreement with the

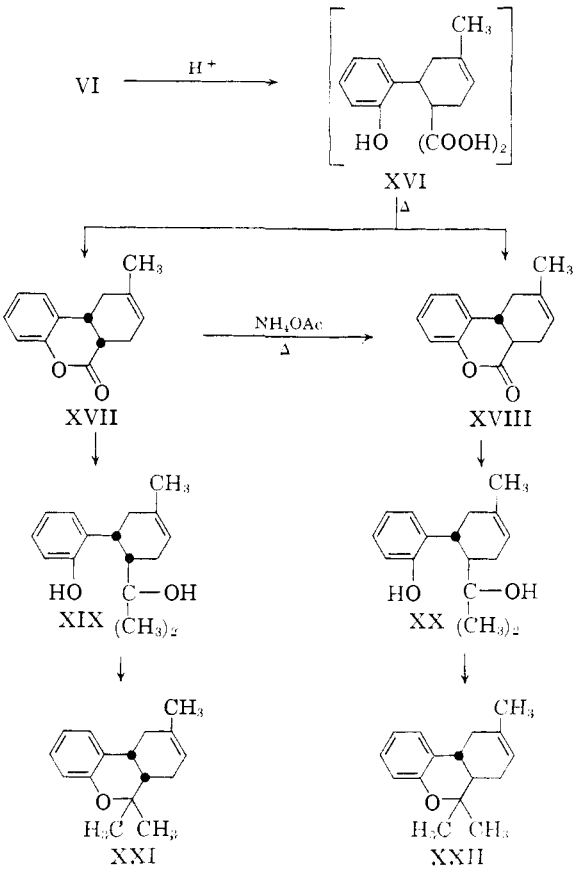
(10) L. Mascarelli and B. Lango, *Gazz. chim. ital.*, **68**, 121 (1938).

prediction, based on an inspection of the models, that the *cis* isomer should undergo predominately stereospecific addition to the less hindered side of the cyclohexene ring (away from the benzene ring) to give a single adduct, while the more planar *trans* isomer should undergo addition equally well at either side of the cyclohexene ring to give a mixture of adducts.

Treatment of the lactones XVII and XVIII with an excess of methylmagnesium iodide yielded *cis*- and *trans*-1-methyl-4-(α-hydroxy-α-methylethyl)-5-(*o*-hydroxyphenyl)-1-cyclohexene (XIX and XX), respectively. Subsequent cyclization by heating in xylene in the presence of *p*-toluenesulfonic acid afforded *cis*- and *trans*-6,6,9-trimethyl-6a,7,10,10a-tetrahydrodibenzopyran (XXI and XXII), the desired tetrahydrocannabinol models.

Attempted cyclization of XIX and XX with thionyl chloride led to the simultaneous formation of chlorine-containing products which are presumably the result of hydrogen chloride addition to the alicyclic double bond.

The question of possible double bond migration in the course of the above conversions of VI to XXI and XXII must be considered. From an inspection of the ultraviolet absorption spectra of all compounds prepared in this sequence (see Experimental), it can be said with certainty that no migration of the 8,9-double bond to a conjugated position has taken place. Moreover, the close similarity of the positions of the absorption maxima as well as the value of the extinction coefficients throughout each series indicates that the double bond has remained in the same position throughout the conversions. The appearance of two additional absorption maxima in the spectrum of the *cis* product XXI indicates that the product obtained was impure. It seems probable that, in this case, some double bond migration may have occurred during the final acid-catalyzed cyclization step, although not to a position conjugated with the aromatic ring.



Experimental[11]

3-Cyanocoumarin (III) was prepared essentially by the procedure of Baker and Howes[12] except that the intermediate *o*-hydroxybenzylidenemalononitrile was not isolated. Instead, the crude condensation mixture was hydrolyzed directly with 4 *N* hydrochloric acid to give 3-cyanocoumarin in an over-all yield of 87%.

6a-Cyano-9-methyl-6a,7,10,10a-tetrahydro-6-dibenzopyrone (V).—A mixture of 20 g. of 3-cyanocoumarin, 16 g. of freshly distilled isoprene, 40 ml. of xylene and a few crystals of hydroquinone was heated in a steel reaction vessel at 180–186° for 7 hours. Evaporation of the light brown liquid gave an oily residue which was recrystallized from carbon tetrachloride until a constant melting point was obtained; yield 11.8 g. (42%), m.p. 93–95°. The product was purified for analysis by sublimation at 90°(0.04 mm.).

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.3; H, 5.5; N, 5.85. Found: C, 75.45; H, 5.6; N, 5.9.

6a-Carbethoxy-9-methyl-6a,7,10,10a-tetrahydro-6-dibenzopyrone (VI).—A mixture of 50 g. of 3-carbethoxycoumarin, 36 g. of freshly distilled isoprene, 50 ml. of xylene and a few crystals of hydroquinone was heated in a steel reaction vessel at 220° for 8 hours with continuous rocking. Evaporation of the reaction mixture under reduced pressure and recrystallization of the residue to constant melting point gave 25.8 g. (39%) of white crystals, m.p. 107–108°. A sample was purified for analysis by sublimation at 105° (0.04 mm.).

Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.3; H, 6.3. Found: C, 71.05; H, 6.3.

9-Methyl-6-dibenzopyrone (VII).—A mixture of 0.5 g. of 6a-cyano-9-methyl-6a,7,10,10a-tetrahydro-6-dibenzopyrone and 1.0 g. of 30% palladium-on-carbon was heated at 210° for 30 minutes. The product was removed from the mixture by sublimation at 210°(0.10 mm.) to give 0.17 g. (35%) of a white crystalline solid, m.p. 101–103°.

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 80.0; H, 4.8. Found: C, 80.2; H, 4.9.

The same product was obtained in 41% yield from 6a-carbethoxy-9-methyl-6a,7,10,10a-tetrahydro-6-dibenzopyrone by the method described above. The identity of the products was established by a mixture melting point determination and by comparison of infrared spectra.

2,5-Dimethyl-2′-nitrobiphenyl (X).—A solution of *o*-nitrobenzenediazonium chloride was prepared in the usual manner from 104 g. of *o*-nitroaniline and added to 325 ml. of pure *p*-xylene (m.p. 13–14°) which was cooled in an ice-bath. A solution of 170 g. of sodium acetate in 800 ml. of water was added slowly to this mixture over the course of 1 hour. The reaction mixture was then stirred for 36 hours, with the temperature maintained at 10–15° for the first few hours and at room temperature for the remainder of the time. The aqueous layer was discarded and the black organic layer diluted with 1 l. of ether and washed twice with 10% sodium hydroxide and then 4 times with water. The organic layer was evaporated to remove the ether and the residue steam distilled. Xylene came off first, followed by a yellow liquid with a nitrobenzene odor. After the nitrobenzene odor could no longer be detected in the distillate, the pot was heated in an oil-bath to 150° and steam distillation was continued for an additional 8 hours. The distillate was collected in two 2-l. fractions and the organic product in each fraction was recovered by extraction with ether. The ether extracts were dried over magnesium

(11) We are indebted for the microanalyses to Mr. Joseph Nemeth, University of Illinois. All melting points are corrected. Infrared spectra of all compounds prepared are on file at the University of Illinois.

(12) W. Baker and C. S. Howes, *J. Chem. Soc.*, 119 (1953).

sulfate, the ether removed by distillation and the red residual liquid (6.5 g.) purified by distillation at 90°(0.05 mm.).

Anal. Calcd. for $C_{14}H_{12}NO_2$: C, 74.0; H, 5.8. Found: C, 73.85; H, 5.6.

2,5-Dimethyl-2'-hydroxybiphenyl (IX). Method A.—A solution of 5.8 g. of 2,5-dimethyl-2'-nitrobiphenyl in 50 ml. of absolute ethanol was hydrogenated at 3 atmospheres pressure at room temperature in the presence of 1 g. of Raney nickel. Hydrogen uptake was completed in 1 hour. The Raney nickel was removed by filtration and the filtrate evaporated under reduced pressure to give a brown liquid. A solution of 3 g. of this liquid (2,5-dimethyl-2'-aminobiphenyl) in 25 ml. of 10% sulfuric acid was cooled to 0° and treated with 1.0 g. of sodium nitrite dissolved in 10 ml. of water. The resulting diazonium salt solution was filtered and to the filtrate was added 16 ml. of concentrated sulfuric acid. The resulting mixture was heated under reflux for 45 minutes. Cooling caused the separation of **3-methylfluorene (XII)**, which was collected by filtration and purified by sublimation at 80°(0.05 mm.). The material melted at 91–92° (reported[10] m.p. 88–89°).

Anal. Calcd. for $C_{14}H_{12}$: C, 93.3; H, 6.7. Found: C, 93.4; H, 6.9.

The filtrate was extracted with hexane and the hexane extract in turn was extracted with several portions of Claisen alkali to separate the desired 2,5-dimethyl-2'-hydroxybiphenyl from any remaining 3-methylfluorene. The aqueous alkaline layer was acidified with dilute sulfuric acid and then extracted with ether. The ether layer was washed with water, dried over magnesium sulfate, the ether evaporated and the residual oil distilled at 90°(0.05 mm.).

Anal. Calcd. for $C_{14}H_{14}O$: C, 84.8; H, 7.1. Found: C, 84.6; H, 7.1.

Method B.—To a solution of 0.13 g. of lithium aluminum hydride in 25 ml. of dry ether was added a solution of 0.70 g. of 9-methyl-6-dibenzopyrone in 40 ml. of dry ether. The mixture was stirred at room temperature for 2 hours and excess lithium aluminum hydride was then destroyed by the addition of a mixture of 20 ml. of ether and 5 ml. of methanol. The reaction mixture was washed several times with water, the ether layer dried over magnesium sulfate and the ether removed by evaporation. The residue was dissolved in 25 ml. of ethanol and the resulting solution hydrogenated for 12 hours under 3 atmospheres of hydrogen in the presence of 0.30 g. of 5% palladium chloride-on-carbon. Removal of the catalyst and concentration of the filtrate gave a residual brown liquid which was distilled at 90°(0.05 mm.). The products obtained by methods A and B were identical as determined by a comparison of their infrared spectra.

1-Methyl-4-cyano-4-(α-hydroxy-α-methylethyl)-5-(*o*-hydroxyphenyl)-1-cyclohexene (XIII).—A solution of methylmagnesium iodide was prepared from 10.0 g. of magnesium turnings, 57 g. of methyl iodide and 400 ml. of dry ether and added over the course of 1 hour to a solution of 23.7 g. of 6a-cyano-9-methyl-6a,7,10,10a-tetrahydro-6-dibenzopyrone in 450 ml. of dry ether. The reaction mixture was stirred at room temperature for 6 hours, and then both the gummy precipitate which had separated and the supernatant ether layer were treated cautiously with ice-cold dilute sulfuric acid. The ether layer was separated, washed with 1 l. of water, dried over magnesium sulfate and the ether evaporated. Recrystallization of the residual solid yielded 18.8 g. (70%) of white crystals, m.p. 162–164°. A sample was purified for analysis by sublimation at 150°(0.05 mm.).

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.2; H, 7.8; N, 5.2. Found: C, 75.25; H, 7.55; N, 5.4.

6a-Cyano-6,6,9-trimethyl-6a,7a,10,10a-tetrahydrodibenzopyran (XIV).—A mixture of 4.37 g. of 1-methyl-4-cyano-4-(α-hydroxy-α-methylethyl)-5-(*o*-hydroxyphenyl)-1-cyclohexene and 20 ml. of pure thionyl chloride was refluxed on a steam-bath for 2 hours. The excess thionyl chloride was removed by distillation, 50 ml. of water added to the residue, and the cooled solution extracted with 100 ml. of ether. The ether extract was washed with water, dried over magnesium sulfate and evaporated. Distillation of the residue at 155–160°(0.5 mm.) gave a small amount of a clear, viscous oil.

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.6; H, 7.6; N, 5.5. Found: C, 80.3; H, 7.4; N, 5.3.

All attempts to hydrolyze the cyano group of XIV, *i.e.*, with a mixture of sulfuric and acetic acid at 100° for 59 hours, 50% sulfuric acid at 140° for 2 hours, hot polyphosphoric acid or alkaline hydrogen peroxide, led to the formation of pale yellow crystals, m.p. 126–127°, isomeric with XIV and still retaining the cyano group.

Anal. Calcd. for $C_{17}H_{19}NO$: C, 80.6; H, 7.6; N, 5.5. Found: C, 80.5; H, 7.5; N, 5.8.

4-Methyl-6-(*o*-hydroxyphenyl)-Δ³-tetrahydrobenzoic Acid (XV).—A solution of 7.4 g. of 9-methyl-6a-cyano-6a,7,10,10a-tetrahydro-6-dibenzopyrone in 100 ml. of 50% sulfuric acid and 30 ml. of acetic acid was heated at 100° for 14 hours, the acetic acid removed by evaporation under reduced pressure and the residual solution extracted with ether. The ether extracts were washed with a saturated sodium carbonate solution, the washings were acidified with 50% sulfuric acid and in turn extracted with ether. Evaporation of the ether yielded a red, viscous oil which was distilled at 100–170°(0.1 mm.). During the initial stages of the heating, considerable bubbling took place, and when it had subsided the temperature was slowly raised to 170°. White, rock-like crystals mixed with a little yellow oil were obtained. Recrystallization of the crystals from aqueous ethanol followed by sublimation at 150°(0.1 mm.) gave a small amount of a colorless solid, m.p. 193–195°.

Anal. Calcd. for $C_{14}H_{18}O_3$: C, 72.4; H, 6.95. Found: C, 72.6; H, 7.0.

***cis*- and *trans*-9-Methyl-6a,7,10,10a-tetrahydro-6-dibenzopyrone (XVII and XVIII).**—A mixture of 10.0 g. of 6a-carbethoxy-9-methyl-6a,7,10,10a-tetrahydro-6-dibenzopyrone (VI), 5.0 g. of sodium hydroxide, 50 ml. of water and 50 ml. of ethanol was heated under gentle reflux for 18 hours. Removal of the ethanol by evaporation under reduced pressure followed by acidification of the residual solution to *p*H 1 yielded 13.0 g. of a pale pink solid. This solid was added to 80 ml. of xylene in a flask fitted with a Dean–Stark trap, and the mixture was heated under reflux for 12 hours. Evaporation of the xylene under reduced pressure and sublimation of the residue gave 6.75 g. (91%) of white crystals melting over a broad range (80–145°). Fractional crystallization of this material from ethanol yielded 1.54 g. (20%) of the more soluble *cis* isomer, m.p. 95.5–97°, and 1.88 g. (25%) of the less soluble *trans* isomer, m.p. 143–144°.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.5; H, 6.6. Found (*cis* isomer): C, 78.5; H, 7.0. (*trans* isomer): C, 78.7; H, 6.6.

Isomerization of XVII to XVIII.—A mixture of 0.42 g. of *cis*-9-methyl-6a,7,10,10a-tetrahydro-6-dibenzopyrone and 2 g. of ammonium acetate was heated at 250° for 30 minutes. Additional ammonium acetate was added as acetamide formed and distilled from the flask. The cooled reaction mixture was treated with 100 ml. of water and the insoluble solid collected by filtration. Recrystallization from ethanol gave 0.1 g. of white crystals, m.p. 143–144°, identical with a pure sample of the *trans*-lactone XVIII.

Addition of Hydrogen Bromide to *cis*-9-Methyl-6a,7,10,10a-tetrahydro-6-dibenzopyrone (XVII).—Dry hydrogen bromide was bubbled for 4 minutes through a cooled (−5°) solution of 1.0 g. of XVII in 230 ml. of purified petroleum ether (30–40°). The reaction mixture was allowed to stand for 35 minutes at −5°, and then the petroleum ether was removed by evaporation under reduced pressure to give 1.12 g. (81%) of white needles, m.p. 138–140°. Recrystallization from hexane did not change the melting point.

Anal. Calcd. for $C_{14}H_{15}BrO_2$: C, 57.0; H, 5.1. Found: C, 57.2; H, 4.8.

Addition of Hydrogen Bromide to *trans*-9-Methyl-6a,7,10,10a-tetrahydro-6-dibenzopyrone (XVIII).—Treatment of XVIII with hydrogen bromide as described above gave 1.33 g. (96.5%) of tan crystals, m.p. 122–130°. Repeated recrystallization from hexane gave colorless crystals, m.p. 138–139°; a mixture of this material and the hydrogen bromide adduct to the *cis* isomer (m.p. 138–140°) melted at 108–125°.

Anal. Calcd. for $C_{14}H_{15}BrO_2$: C, 57.0; H, 5.1. Found: C, 57.6; H, 5.4.

***cis*-1-Methyl-4-(α-hydroxy-α-methylethyl)-5-(*o*-hydroxyphenyl)-1-cyclohexene (XIX).**—To a solution of methylmagnesium iodide (prepared from 0.65 g. of magnesium turnings, 4.0 g. of methyl iodide and 50 ml. of ether) was added a solution of 1.45 g. of *cis*-9-methyl-6a,7,10,10a-tetrahydro-6-dibenzopyrone and the mixture was stirred at room temperature for 8 hours. To it was then added 75

ml. of ice-water containing 1.5 ml. of sulfuric acid, and the ether layer was separated, washed with water and dried over magnesium sulfate. Evaporation of the ether followed by sublimation of the residue at 120°(0.05 mm.) gave 1.30 g. (78%) of white crystals, m.p. 139–140.5°; λ_{max}^{EtOH} 275, 282 mμ; log ε 3.38, 3.33.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.0; H, 9.0. Found: C, 78.3; H, 9.3.

trans-1-Methyl-4-(α-hydroxy-α-methylethyl)-5-(*o*-hydroxyphenyl)-1-cyclohexene (XX) was prepared in 81% yield by the method described above, starting with the *trans*-lactone XVIII. The product was obtained as white crystals, m.p. 137.5–138°. A mixture of this material and the corresponding *cis* isomer above (m.p. 139–140.5°) melted at 112–126°; λ_{max}^{EtOH} 276, 283 mμ; log ε 3.42, 3.36.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.0; H, 9.0. Found: C, 77.95; H, 9.0.

cis-6,6,9-Trimethyl-6a,7,10,10a-tetrahydrodibenzopyran (XXI).—A mixture of 2.33 g. of *cis*-1-methyl-4-(α-hydroxy-α-methylethyl)-5-(*o*-hydroxyphenyl)-1-cyclohexene, 20 ml. of toluene and 0.05 g. of *p*-toluenesulfonic acid was heated under reflux for 2.5 hours. During this time the color of the reaction mixture changed from pink to dark yellow. The cooled reaction mixture was diluted with 100 ml. of ether and the solution washed twice with 100-ml. portions of 10% potassium carbonate and 3 times with water. The organic layer was dried and evaporated to give a residual oil which was rapidly distilled at a pot temperature of 175° and under 0.5 mm. pressure to give 1.29 g. (60%) of a clear liquid; λ_{max}^{EtOH} 268, 275, 284, 306 mμ; log ε 3.49, 3.48, 3.39, 3.20. The ultraviolet data indicate that this product is not homogeneous. It appears to consist largely of XXI, along with isomeric material probably arising from double bond migration, although not to a position conjugated with the aromatic ring.

Anal. Calcd. for $C_{16}H_{20}O$: C, 84.2; H, 8.8. Found: C, 83.9; H, 8.7.

trans-6,6,9-Trimethyl-6a,7,10,10a-tetrahydrodibenzopyran (XXII) was prepared in 75% yield from the *trans*-diol XX by the method described above. The product was obtained in the form of white crystals, m.p. 63.3–64.3° upon recrystallization from methanol; λ_{max}^{EtOH} 276, 284 mμ; log ε 3.42, 3.40.

Anal. Calcd. for $C_{16}H_{20}O$: C, 84.2; H, 8.8. Found: C, 84.2; H, 8.9.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BRANDEIS UNIVERSITY, WALTHAM 54, MASS.]

Synthesis of Cyclized Derivatives of New Secondary Nitrogen Mustards Relationship of Structure to Toxicity[1a,b]

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RECEIVED MARCH 2, 1960

Two new cyclic mustards 1-(2′-chloroethyl)-2-chloromethylpiperidine and 1-(2′-chloroethyl)-2-chloromethylhexamethyleneimine have been synthesized. The former was also formed when the acyclic secondary nitrogen mustard, 5-chloro-1-(chloromethyl-*n*-pentyl)-2-chloroethylamine hydrochloride, was heated in phosphorus oxychloride. On similar treatment the homologous acyclic mustard did not give the latter but simply gave a rearranged product, presumably 2,7-dichloro-*n*-hexyl-2′-chloroethylamine hydrochloride. The piperidine mustard was highly toxic in mice whereas the hexamethyleneimine mustard was less so [1.4 and 0.3 times, respectively, as methyl-bis-(β-chloroethyl)-amine].

In previous publications[2a,b] we have described the preparation of a new type of secondary amino nitrogen mustards that transformed spontaneously by intramolecular cyclization to tertiary nitrogen mustards *in vivo*. These new mustards were expected to be substantially more cytotoxic than the usual secondary nitrogen mustards and, in fact, have been found to be so.[3] These mustards were developed for the synthesis of derivatives with greater selectivity in their toxicity for tumor cells than the nitrogen mustards are generally known to have. Thus nitrogen mustards detoxified by N-phosphorylation,[1,2,4a,b] N-acylation[5] and possibly by other forms of N-substitution that might be reactivated by removal of the blocking group more or less selectively in tumor cells[6a,b] are potentially even more effective chemotherapeutic agents than are the parent mustards.

It is of incidental interest that the cyclizeable nitrogen mustards IV, VII and VIII (*vide infra*) have shown significant anti-tumor activity in a variety of experimental tumors in animals.[7] One of the factors that may contribute to their activity is the "time-fuse" mechanism imposed on their action by the time required for activation by cyclization after administration. This may allow these compounds time to reach cancer cells remote from the site of injection in active form.

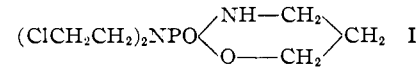
From a comparison of the acute toxicity (as measured by LD_{50} in mice) of these cyclizeable nitrogen mustards with that of the cyclic analogs into which they are presumed to transform *in vivo* certain inferences as to their mode of action can be drawn. From previous results,[3] for example, it appeared that the difference in toxicity between the acyclic trichloroamines II and IV was probably related to the difference in amounts of cyclized com-

(1)(a) This investigation was supported by a research grant (No. CY2130) from the National Institutes of Health, U. S. Public Health Service; (b) presented at the American Chemical Society Meeting, Cleveland, April, 1960.

(2) (a) O. M. Friedman and E. Boger, THIS JOURNAL, **78**, 4659 (1956); (b) O. M. Friedman and A. M. Seligman, *ibid.*, **76**, 658 (1954).

(3) A. M. Rutenburg, L. Persky, O. M. Friedman and A. M. Seligman, *J. Pharm. Exp. Therap.*, **3**, 483 (1954).

(4) (a) O. M. Friedman and A. M. Seligman, THIS JOURNAL, **76**, 655 (1954). (b) Recently the cyclic phosphorodiamidate I, a "transport" form of nor-HN2 which is presumably transformed to the "active" form at the site of action has shown a high therapeutic index against experimental tumors in animals and has given positive results against some forms of human cancer [R. Gross and K. Lambers, *Naturwiss.*, **45**, 66 (1958); for a recent review see also Cancer Chemotherapy Reports, June, 1959, CCNSC, U. S. Public Health Service]. We have prepared the analogous derivatives of the cyclizable nitrogen



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mustards IV, VII and VIII which will be reported elsewhere.

(5) O. M. Friedman and R. Chatterji, THIS JOURNAL, **81**, 3750 (1959).

(6) (a) E. Boger and O. M. Friedman, *ibid.*, **80**, 2583 (1958); (b) A. M. Seligman, M. M. Nachlas, L. H. Mannheimer, O. M. Friedman and G. Wolf, *Ann. Surg.*, **130**, 333 (1949).

(7) Unpublished results from the Childrens Cancer Research Foundation, Boston, Mass., and the CCNSC Screening Program, N.I.H., U. S. Public Health Service.