

The Separation of *cis* and *trans* Diacetates of Cyclohexane-1,4-diol

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The cyclohexane-1,4-diols have been rather extensively studied by several workers. Bayer^{1a} reported the separation of the *cis* and *trans* forms through the diacetates, and gave the melting point of the *cis* form of the diacetate as 34–36°. Palfray and Rothstein have also investigated the cyclohexanediols extensively.² However, it was not until 1938 that Coops, Dienske and Aten³ reported the successful separation of pure *cis*-cyclohexane-1,4-diol by employing the ditrityl ether. The pure *cis* diol melts at 112°, the diacetate at 39°. These workers showed that the diacetates formed a minimum melting eutectic composed of about 16% *trans* and 84% *cis*, melting at about 34°. They demonstrated that Bayer's *cis* diacetate of m.p. 34–36° contained 17% of *trans* isomer. Mixed melting point curves were given for the diacetates, ditrityl ethers and the free diols.

In the course of other work, we have had occasion to prepare pure *cis*-cyclohexane-1,4-diol. We have found that this may conveniently be accomplished by crystallizing a *cis-trans* mixture of the diacetates from petroleum ether, b.r. 30–60°, in conjunction with a rather simple mechanical separation. Since this separation avoids the use of the expensive trityl chloride, and also because confusion exists in the literature as to the nature of the pure *cis* diol,⁴ we are reporting our results at this time.

X-Ray powder diffraction analyses of the *cis* and *trans* diacetates of cyclohexane-1,4-diol show the two forms to be distinctly different (Fig. 1).

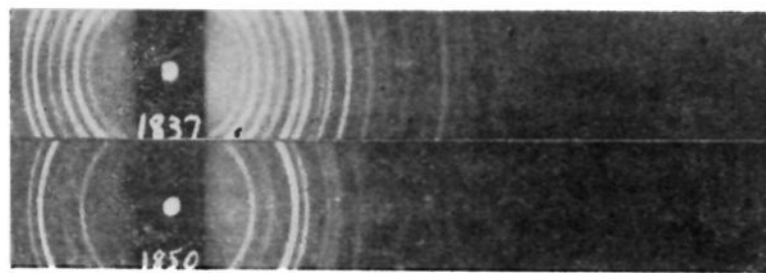


Fig. 1.—X-Ray powder diffraction patterns of *cis* (1837) and *trans* (1850) cyclohexane-1,4-diol diacetates.

The eutectic form at about 16% *trans* and 84% *cis* proved to be a simple mixture of the isomers. A prepared mixture containing 5% of the *trans* form and 95% *cis* indicated that a content of 2% or less of the *trans* isomer could be detected by X-ray powder diffraction analysis in a mixture of the two forms. The X-ray diffraction patterns

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(1a) Bayer, *Ann.*, **278**, 92 (1894).

(2) One of the most extensive papers in this field is that of Rothstein in *Ann. Chim.*, **14**, 461–598 (1930).

(3) Coops, Dienske and Aten, *Rec. trav. chim.*, **57**, 303–315 (1938).

(4) Olberg, Pines and Ipatieff, *THIS JOURNAL*, **66**, 1096–1099 (1944).

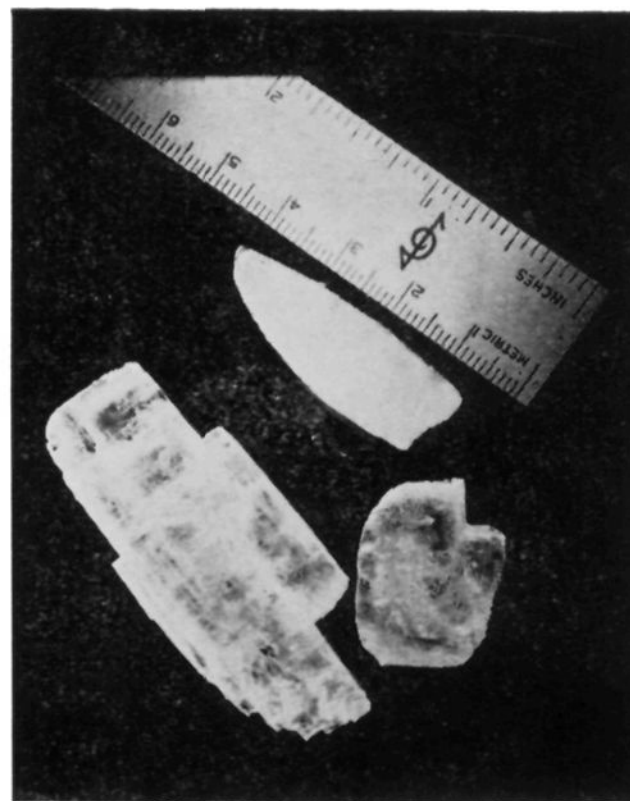


Fig. 2.—Crystals of *cis*-cyclohexane-1,4-diol diacetate.

were obtained using a commercial X-ray diffraction unit utilizing a copper target with a 0.00035 in. nickel filter giving essentially $\text{CuK}\alpha$ radiation. The powdered sample was mounted on a wedge-type holder at the center of a cylindrical camera of 14.32 cm. diameter. The X-ray powder diffraction data are given in the conventional manner in

<i>d</i> ^a	<i>Cis</i>	<i>I/I</i> ₀ ^b	<i>d</i>	<i>Trans</i>	<i>I/I</i> ₀
7.2		0.21	6.6		0.25
6.24		.76	5.62		.03
5.36		.55	5.32		.09
4.76		.22	4.40		1.00
4.24		1.00	4.04		0.37
3.90		0.60	3.51		.18
3.56		.10	3.36		.15
3.42		.28	3.30		.23
3.09		.50	3.23		.15
2.92		.01	2.93		.16
2.88		.04	2.85		.07
2.75		.15	2.79		.06
2.63		.04	2.67		.04
2.56		.06	2.37		.01
2.38		.06	2.29		.03
2.33		.06	2.13		.03
2.18		.06	2.03		.04
2.05		.18	1.94		.03
1.97		.06	1.86		.01
1.89		.04	1.80		.20
1.78		.02	1.75		.01
1.75		.06	1.70		.03
1.65		.01	1.60		.01
1.60		.01			
1.57		.01			

^a *d* is the interplanar spacings in ångström units.
^b *I/I*₀ gives the relative intensities of the lines as measured with a recording microphotometer.

Table I. The X-ray crystallography of the *trans* diacetate has been reported by T. N. White.⁵

Experimental

Cyclohexanediol⁶ (471 g.), prepared by the catalytic hydrogenation of hydroquinone, was acetylated with 8.12 equivalents of acetic anhydride by refluxing two hours. The acetylation mixture was allowed to stand at room temperature several days. The volatile material was distilled off at 10 mm. on the steam-bath. The distillate weighed 620 g. The residue crystallized on cooling. The diacetate crystals were filtered at 38°, washed twice with a small amount of alcohol and dried *in vacuo*, m. p. 102.5–103.5°.

The mother liquors were poured into water, extracted with ether, dried with anhydrous potassium carbonate, the ether removed and the residue crystallized from about 300 cc. of alcohol. The first crop weighed 280 g. This material was crystallized from petroleum ether (b. r. 30–60°) (Skellysolve "F"). Two forms of crystals were obtained. The *trans* form crystallized as fragile needles, while the *cis* form came down as massive prisms or as rosetts. By vigorously shaking the dried product the *trans* crystals were broken up and the *cis* form was easily picked out. The crude *cis* form thus obtained melted at 35–37°. This was dissolved in petroleum ether, and when cold seeded with a well-formed *cis* crystal. The *cis* form crystallized at once. By carefully watching the course of the crystallization it was easy to observe the formation of the first needles of the *trans* diacetate. At this point the liquid was decanted from the *cis* crystals. One or two more crystallizations from petroleum ether sufficed to remove impurities and to yield a *cis* form with a freezing point of 41.25°. Coops, *et al.*, give 39° as the melting point of this isomer. Typical crystals are shown in Fig. 2. The refractive index of the pure *cis* form (supercooled liquid) was n_D^{25} 1.4508 and n_D^{25} 1.4518. The b. p. at 760 mm. was 251°.

Anal. Calcd. for $C_{10}H_{16}O_4$ (*cis*): mol. wt., 200.23; C, 59.98; H, 8.06. Found: C, 60.25; H, 7.98.

Hydrolysis was accomplished by boiling for four hours with four times the weight of barium hydroxide octahydrate in 25 volumes of water. Carbon dioxide was passed in to precipitate excess barium, and the solution filtered, evaporated to dryness, and extracted with acetone. The acetone was concentrated, filtered and the solution allowed to crystallize. The product melted at 112.4–112.8°.

Coops, *et al.*, give 112° as the melting point of the pure *cis* form.

(5) T. N. White, *Z. Krist.*, **80**, 5–17 (1931).

(6) We are indebted to Dr. Nathan L. Drake, at University of Maryland, for supplying us with a generous amount of cyclohexane-1,4-diol.

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The Preparation of 10-Chloro-7-(3-Diethylaminopropylamino)-pyrid[3,2-*c*]acridine¹

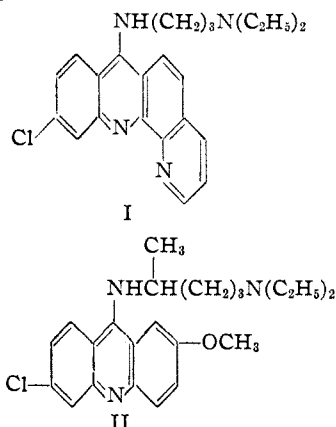
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During the recent search for new antimalarials it seemed of interest to prepare for testing 10-

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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chloro-7-(3-diethylaminopropylamino)-pyrid[3,2-*c*]acridine (I), which is closely related chemically to atebirin (II) but which has the additional heterocyclic ring.



By the use of experimental conditions similar to those employed³ in the condensation of *p*-anisidine with 2,5-dichlorobenzoic acid, 8-aminoquinoline was condensed with 2,4-dichlorobenzoic acid to give 8-(2-carboxy-5-chlorophenylamino)-quinoline in 55% yield. This substance readily underwent the expected cyclization and the product reacted with phosphorus oxychloride to form 7,10-dichloropyrid[3,2-*c*]acridine in 38% yield. The desired drug (I) was obtained by heating the dichloro compound with 3-diethylaminopropylamine at 100–110° for two hours; it was isolated only as the picrate. Because of the fact that it became necessary to abandon the project before the synthesis could be repeated on a preparative scale, the work is being reported in its present form.

Experimental

8-(2-Carboxy-5-chlorophenylamino)-quinoline.—A 150-ml. three-necked flask, fitted with a stirrer and a partial reflux condenser, containing 15 g. of 8-aminoquinoline, 14.3 g. of 2,4-dichlorobenzoic acid, 10.4 g. of potassium carbonate, 0.05 g. of copper bronze and 30 ml. of *n*-hexanol was placed in an oil-bath. The contents were well stirred and the temperature of the oil-bath was kept at 180°. After the solution had been heated for about twenty minutes the contents solidified; however, the mixture was heated for an additional two hours at the above temperature. The pasty brown solid was added to water and the mixture was steam distilled. The brown solution (400 ml.) remaining in the distilling flask was filtered while hot and as the solution cooled the green potassium salt precipitated. After additional water had been added, the mixture was heated to boiling to dissolve the salt. The solution was made acidic with acetic acid and the green solid was collected by filtration and washed with water. The crude product after being dried in an oven at 80° weighed 13 g. (55%).

The substance after recrystallization from xylene melted at 246–249°.

Anal. Calcd. for $C_{16}H_{11}O_2ClN_2$: C, 64.23; H, 3.71. Found: C, 64.45; H, 3.71.

10-Chloro-7-hydroxy-pyrid[3,2-*c*]acridine.—In a 50-ml. flask was placed a mixture of 7 g. of crude 8-(2-carboxy-5-chlorophenylamino)-quinoline and 12 ml. of

(3) Feldman and Kopeliowitsch, *Arch. Pharm.*, **273**, 488 (1935).