

600  $\mu$  and time was a linear function (Fig. 2). The convertibility of dihydronorkynuramine to indigo did not exceed  $\sim 30\%$  in a given experiment. For quantitative assays of monoamine oxidase kynuramine is superior although the enzymatic formation of indigo may serve as a qualitative visual test for the presence of monoamine oxidase.

It was of interest to test dihydronorkynuramine as a histochemical agent for staining tissue *in situ* and thus localize the areas containing monoamine oxidase. Microscopic inspection of liver and kidney slices incubated with dihydronorkynur-

amine showed the formation of the unmistakable dark blue indigo crystals. However these crystals formed only in solution and did not combine with the protein fibre. It may be possible that a useful histochemical stain may be developed along these lines, if suitable binding groups are introduced into the benzene part of dihydronorkynuramine. For example, halogens in positions 4 and 5 of indoxyl derivatives are known to increase the substantivity of the resulting indigo dyes.<sup>10</sup>

The oxidative degradation of L-kynurenine by snake venom L-amino acid oxidase to kynurenic acid has been developed into a convenient spectrophotometric assay of that enzyme.<sup>11</sup> The analogous reaction of *o*-amino-erythro-DL-phenylserine with snake venom L-amino acid oxidase did not lead to any uptake of oxygen and therefore not to a colored product, arising possibly from the expected indoxyl-2-carboxylic acid.

**Acknowledgment.**—We are greatly obliged to Dr. George G. Glenner, Laboratory of Pathology, NIAMD, for his help and advice on the histochemical tests.

(10) H. C. F. Su and K. C. Tsou, *THIS JOURNAL*, **82**, 1187 (1960).

(11) H. Weissbach, A. V. Robertson, B. Witkop and S. Udenfriend, *Anal. Biochem.*, in press.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY, STANFORD, CALIF.]

## Optical Rotatory Dispersion Studies. XLI.<sup>1</sup> $\alpha$ -Haloketones (Part 9).<sup>2</sup> Bromination of Optically Active *cis*-1-Decalone. Demonstration of Conformational Mobility by Rotatory Dispersion<sup>3</sup>

BY CARL DJERASSI AND J. STAUNTON<sup>4</sup>

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*cis,cis*-1-Decalol (IV) has been resolved for the first time through its  $3\beta$ -acetoxy- $\Delta^4$ -etienate (III) and a convenient preparation of the resolving agent,  $3\beta$ -acetoxy- $\Delta^4$ -etienic acid (II), is reported. The absolute configurations of the derived (-)-*cis*-1-decalone (V) and (-)-*trans*-1-decalone (VI) were established by comparing their rotatory dispersion curves with those of their 10-methyl analogs of known relative and absolute stereochemistry. Bromination of (-)-*cis*-1-decalone afforded in pure form all six possible monobromo-*cis*- and *trans*-1-decalones, whose rotatory dispersion curves were fully consistent with the assigned structures (VII–XII). Measurement of the rotatory dispersion curve of the axial (-)-2 $\alpha$ -bromo-*cis*-1-decalone (XI) in solvents of different polarity demonstrated the existence of a 70–30 equilibrium between the "steroid" (XIa) and "non-steroid" (XIb) conformations of this ketone.

Recently, Zimmerman and Mais,<sup>5</sup> in connection with their studies on the stereochemistry of the ketonization process, investigated the bromination of *cis*-1-decalone. Of the six possible monobromo ketones (VII–XII),<sup>6</sup> they were able to isolate four (VII–X) in pure form and probably a fifth one (XII) in an impure state. Their structural assignments were based on infrared measurements (thus differentiating axial from equatorial isomers<sup>7</sup>), ther-

modynamic considerations and finally debromination as well as dehydrobromination experiments. While these elegant experiments<sup>5</sup> were quite self-consistent, it nevertheless seemed worth while to reinvestigate this bromination with optically active *cis*-1-decalone in order to apply rotatory dispersion measurements<sup>8</sup> to the various bromo ketones. Extensive rotatory dispersion studies with a variety of  $\alpha$ -halocyclohexanones of known stereochemistry led to the enunciation of the "axial haloketone rule,"<sup>9</sup> which states that introduction of equatorial halogen does not change the sign of the Cotton effect of a cyclohexanone, while an axial bromine

(1) Paper XL, K. Mislow and C. Djerassi *J. Am. Chem. Soc.*, **82**, 5247 (1960).

(2) Part 8, R. Villotti, H. J. Ringold and C. Djerassi, *THIS JOURNAL*, **82**, 5693 (1960).

(3) Supported by grant No. CRTY-5061 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(4) Postdoctorate research fellow, 1959–1960.

(5) H. E. Zimmerman and A. Mais, *THIS JOURNAL*, **81**, 3644 (1959).

(6) Throughout this article we are using absolute configurational representations (*steroid notation*: solid bond ( $\beta$ ) above plane of paper; dotted bond ( $\alpha$ ) below the plane) corresponding to the optical antipode with which we were working.

(7) R. N. Jones, D. A. Ramsey, F. Herling and K. Dobriner, *THIS JOURNAL*, **74**, 2828 (1952); see also E. J. Corey, *ibid.*, **75**, 2301 (1953), as well as E. G. Cummins and J. E. Page, *J. Chem. Soc.*, 3847 (1957).

(8) C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

(9) C. Djerassi and W. Klyne, *THIS JOURNAL*, **79**, 1506 (1957); C. Djerassi, J. Osiecki, R. Riniker and B. Riniker, *ibid.*, **80**, 1216 (1958).

atom governs the sign of the Cotton effect in a predictable manner. Furthermore, the extrema of the Cotton effect of such axial  $\alpha$ -halocyclohexanones are subject to a bathochromic shift<sup>10</sup> of  $20 \pm 5 \mu$  as compared to the halogen-free ketone, in agreement with earlier ultraviolet spectroscopic measurements.<sup>11</sup> The axial haloketone rule has found applications<sup>10</sup> in the solution of structural, conformational and absolute configurational problems and the present case—the bromination of optically active *cis*-1-decalone—poses questions in all three areas. Thus, Zimmerman's<sup>5</sup> differentiation between *trans* (VIII) and *cis* (X) 9-bromo-1-decalone rested largely on thermodynamic considerations and confirmation of these stereochemical assignments by an independent method appeared desirable. Resolution into the optical antipodes immediately raises the question of absolute configuration, while the brominated *cis*-1-decalones present an interesting problem in conformational analysis, which has not been attacked experimentally to any extent. As will be shown in the present article, rotatory dispersion measurements, especially in terms of the axial haloketone rule,<sup>9,10</sup> offer solutions to all of these problems.

In order to apply the optical rotatory dispersion approach, it was first necessary to secure optically active *cis*-1-decalone. Since the resolution of ketones is usually more difficult than that of alcohols,<sup>12</sup> our attention was centered on the resolution of the readily available<sup>13</sup> *cis,cis*-1-decalol (IV).<sup>6</sup> Its resolution has so far not been reported in the literature, but attempted resolution<sup>14</sup> of *cis*-2-decalol has failed using the conventional half-phthalate or camphoric acid methods. Rather than investigate these approaches, we turned directly to the use of the steroid acid,  $3\beta$ -acetoxyetienic acid (II), which has recently been employed<sup>12,15</sup> for the resolution of alcohols; in fact, in one instance<sup>12</sup> this method succeeded where the half-phthalate approach had failed. At one time,  $3\beta$ -hydroxy- $\Delta^5$ -etienic acid was readily available since it represented the key intermediate in the commercial production of deoxycorticosterone. Since then, other approaches starting from 20-keto steroids have largely superseded this process and as substantial amounts of this acid are required if it is to be used widely for resolution purposes, we describe in the Experimental section a satisfactory procedure from the commercially available and cheap pregnenolone acetate (I).

The crude *cis,cis*-1-decalol  $3\beta$ -acetoxy- $\Delta^5$ -etienate (III) crystallized immediately and repeated recrystallization afforded the pure antipode, which was cleaved by means of lithium aluminum hydride to (*-*)-*cis,cis*-1-decalol (IV) and oxidized to (*-*)-*cis*-1-decalone (V).<sup>16</sup> As shown in Fig. 1, the ketone

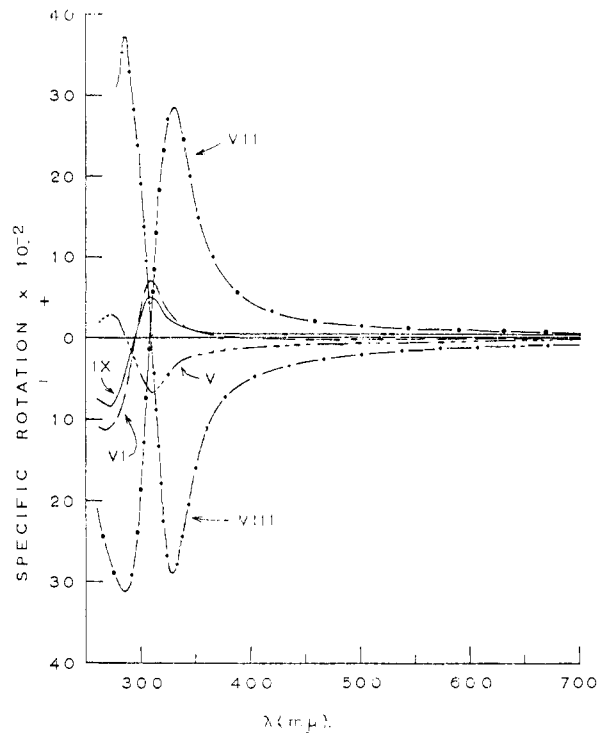


Fig. 1.—Optical rotatory dispersion curves (see footnote 16) in methanol solution: (—)*cis*-1-decalone (V), (---)*trans*-1-decalone (VI), (· · ·)2 $\beta$ -bromo-*trans*-1-decalone (VII), (- · -)9 $\beta$ -bromo-*trans*-1-decalone (VIII) and (- - -)2 $\alpha$ -bromo-*trans*-1-decalone (IX).

exhibited a negative Cotton effect, while acid isomerization gave (*-*)-*trans*-1-decalone (VI) with a positive Cotton effect. This immediately leads to the absolute configurational assignments<sup>5</sup> V and VI since the corresponding 10-methyl analogs of known absolute configuration<sup>17</sup> exhibit similar Cotton effect curves. It should be noted that if we had selected only the negative Cotton effect of (*-*)-*cis*-1-decalone (V), the absolute configurational assignment based on comparison with (*-*)-*cis*-10-methyl-1-decalone would not have been unambiguous, since it has been pointed out<sup>17</sup> that these *cis*-decalones can exist in a steroid (Va) or "non-steroid" (Vb) conformation. We shall return to this conformational problem later on, but such conformational ambiguity does not exist in (*-*)-*trans*-1-decalone (VI) or its 10-methyl analog,<sup>17</sup> where the conformation VI can be accepted safely. This point is important, since a knowledge of the absolute configuration is required in order to use the axial haloketone rule for differentiating between structures VIII and X.

We encountered no difficulties in confirming the results already reported by Zimmerman and Mais<sup>5</sup> by a modified sodium acetate-buffered bromination of racemic *cis*-1-decalone, which furnished four pure monobromo ketones to which structures VII—mately 70% optical purity. Consequently, none of the optical rotatory dispersion results quoted in this paper (except for the analytical specimen of V) refer to 100% optically pure material, but this, of course, is of no consequence as far as structural, absolute configurational or conformational conclusions are concerned (see pp. 135, 142, 206 in ref. 8).

(17) C. Djerassi and D. Marshall, *THIS JOURNAL*, **80**, 3986 (1958).

(10) For summary, see chapter 9 in ref. 8.

(11) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(12) For a recent example see C. Djerassi, E. J. Warawa, R. E. Wolf and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 917 (1960).

(13) W. Hüchel, R. Danneel, A. Gross and H. Naab, *Ann.*, **502**, 99 (1933); W. G. Dauben, R. C. Tweit and C. Mannerskantz, *THIS JOURNAL*, **76**, 4420 (1954).

(14) W. Hüchel and C. Kühn, *Ber.*, **70**, 2479 (1937); L. Mascarelli and D. Dellperl, *Gazz. chim. ital.*, **46**, 416 (1916).

(15) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(16) For the bromination experiments, (*-*)-*cis*-1-decalone was employed which was derived from (*-*)-*cis,cis*-1-decalol (IV) of approxi-

TABLE I

Ketone	R.D. peak (MeOH) <sup>16</sup>			R.D. trough (MeOH) <sup>16</sup>			R.D. amplitude <sup>16</sup>		U.v. (MeOH)		U.v. ( <i>i</i> -octane)		I.r. <sup>4</sup> λ <sub>max</sub>
	[α]	[0]	λ	[α]	[0]	λ	[α]	[0]	λ <sub>max</sub>	log ε	λ <sub>max</sub>	log ε	
V	+ 278	+ 428	272.5	- 657	-1011	309	935	1439	285	1.96	295	1.86	5.84
VI	+ 705	+1086	309	-1130	-1740	267.5	1835	2826	280	1.63	293	1.41	5.83
VII	+2850	+6560	330	-3100	-7130	285	5950	13690	308	2.20	310	1.76	5.83
VIII	+3700	+8510	285	-2900	-6670	328	6600	15180	308	2.02	308	1.78	5.83
IX	+ 500	+1150	308	- 850	-1960	272	1350	3110	280	1.44	280	1.44	5.78
Xa	+3100	+7130	332	-3700	-8150	288	6800	15640	310	2.25	310	2.23	5.83
XIa	+2400	+5520	287.5	-2650	-6100	335	5050	11620	312	2.20	316	2.15	5.83
XIIa	- 94	- 218	294	- 234	- 540	319	140	322	282	1.44	284	1.54	5.79

<sup>a</sup> In methylcyclohexane solution.

Xa had been assigned.<sup>5</sup> Each of these bromo ketones, as well as the two halogen-free parent decalones V and VI, possess characteristic infrared bands (Table II)<sup>18</sup> and when the bromination was repeated with (-)-*cis*-1-decalone (V), identification of the optically active bromo ketones proved to be a simple matter by means of infrared spectroscopy.

Zimmerman and Mais<sup>5</sup> have shown that debromination under non-equilibrating conditions of VII and IX afforded pure *trans*-1-decalone (VI), while similar treatment of VIII and Xa led to a mixture of *cis*- (V) and *trans*- (VI) 1-decalone. They concluded, therefore, that VII and IX represent the isomeric 2-bromo-*trans*-1-decalones and a further differentiation was made possible by infrared measurements indicating an axial orientation for the bromine atom of VII and an equatorial one for IX. As noted in Fig. 1 and Table I, the rotatory dispersion results are in complete agreement with these structures and in fact would have led to these structural conclusions without requiring infrared spectra. The rotatory dispersion curve (Fig. 1) of (+)-2α-bromo-*trans*-1-decalone (IX) is practically identical with that of (-)-*trans*-1-decalone (VI) and since no wave length shift in the extrema is observed, the halogen atom must be equatorial.<sup>9,10</sup> On the other hand, the rotatory dispersion peak of (+)-2β-bromo-*trans*-1-decalone (VII) is moved by 21 mμ toward the visible, thus requiring an axial orientation for the halogen atom. A further criterion<sup>9,10</sup> for the axial character is the greatly increased amplitude of the Cotton effect. The axial haloketone rule<sup>9,10</sup> predicts a strong positive Cotton effect for VII and an equally strongly negative one for the isomer VIII. The positive Cotton effect of VII (Fig. 1) is thus only consistent with the assigned<sup>5</sup> structure VII.

While rotatory dispersion did not offer any information with respect to VII and IX, which was not already available from chemical and infrared studies,<sup>5</sup> a different situation exists with the other two bromo-1-decalones (VIII, X) isolated by Zimmerman and Mais.<sup>5</sup> They showed by infrared means that both ketones contained an axial bromine atom and their debromination experiments led to the conclusion that the halogen atom was situated at C-9. The *trans*-decalone structure VIII was

(18) Zimmerman and Mais (ref. 5) have already listed many of the significant bands of bromo ketones VII-X. Since we have isolated the two additional missing isomers XI and XII and as our measurements were apparently conducted under different conditions, we have collected most of the important infrared bands of the six monobromodecalones VII-XII as well as those of *cis*- (V) and *trans*- (VI) 1-decalone in Table II.

then distinguished from Xa by the observation that the former was more readily dehydrobrominated with collidine and that Xa could be isomerized with hydrogen bromide to VIII. While these last two deductions constitute strong presumptive evidence in favor of the stereochemical assignments, they are not unambiguous. In this instance, rotatory dispersion offers immediate and decisive evidence: the axial haloketone rule predicts a strong negative Cotton effect for (-)-9β-bromo-*trans*-1-decalone (VIII) as was actually found to be the case (Fig. 1). On the other hand, a positive Cotton effect is predicted for (+)-9α-bromo-*cis*-1-decalone (Xa), which again is in agreement with the experimental observation (Fig. 2).

From a conformational standpoint, the three bromo ketones VII, VIII and IX of the *trans*-1-decalone series are uncomplicated, since they can all be expected to be based on conformation VI. However, in the *cis*-1-decalone group, the two conformations Va and Vb have to be considered and the addition of a bromine atom may have an important effect on the relative stability of the two conformers. If the energy difference between the two forms of the α-bromo ketone is only small, then a useful approach is to examine the rotatory dispersion in solvents of differing polarity, such as methanol and isoöctane. Allinger and Allinger<sup>19</sup> have noted that 2α-bromocyclohexanone exists largely in the axial conformation in a non-polar solvent, but that in a polar medium an increased proportion of the equatorial conformer is generated. By applying this observation to optically active α-halocyclohexanones, where the rotatory dispersion curves of the two conformers are different, it should be possible to demonstrate conformational mobility by alterations in the Cotton effect upon changes in the polarity of the solvent and this has indeed been realized.<sup>20</sup>

If we now examine (+)-9α-bromo-*cis*-1-decalone (X) in this light, it will be noted that an axial bromine atom (demonstrated by infrared<sup>5</sup> as well as by the presently recorded ultraviolet and rotatory dispersion measurements) can only be accommodated in the steroid conformation Va, thus leading to the conformational representation Xa. Furthermore, this conformation would be expected<sup>5</sup> to be the preferred one since it contains the electrostatically favored<sup>7,21</sup> axial α-bromo ketone moiety with-

(19) J. Allinger and N. L. Allinger, *Tetrahedron*, **2**, 64 (1958).

(20) C. Djerassi and L. E. Geller, *ibid.*, **3**, 319 (1958); C. Djerassi, L. E. Geller and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 1 (1960); N. L. Allinger, J. Allinger, L. E. Geller and C. Djerassi, *ibid.*, **25**, 6 (1960).

(21) E. J. Corey, *THIS JOURNAL*, **76**, 175 (1954); *Experientia*, **9**, 329 (1953).

out any additional steric complications.<sup>2</sup> Nevertheless, it appeared of interest to see whether there exists any appreciable equilibrium between Xa and the conformer Xb in the "non-steroid" conformation with an equatorial halogen atom. As shown in Table I and the Experimental section, the rotatory dispersion curve of (+)-9 $\alpha$ -bromo-*cis*-1-decalone (X) remained unchanged in either methanol or isoöctane, thus demonstrating that the substance exists exclusively in conformation Xa and that even in the polar solvent methanol none of the conformer Xb with an equatorial bromine atom is produced. As was to be anticipated, the brominated *trans*-1-decalones VIII and IX also showed identical Cotton effect curves in methanol or isoöctane. In view of these results, we feel completely confident that just as in the earlier reported cyclohexanone series,<sup>20</sup> any rotatory dispersion change induced by alterations in the solvent polarity can be attributed to conformational mobility. As shown below, this point is of considerable significance.

In addition to the 9-bromo-*cis*-decalone (Xa), two other monobromo-*cis*-1-decalones (XI, XII) are possible. One of these, XIIa, has probably been obtained earlier<sup>5</sup> in impure form, while the remaining one (XI) is unknown. From our standpoint—examination of conformational situation and mobility by rotatory dispersion—these two compounds are by far the most important ones and we have, therefore, looked for other methods of bromination. Zimmerman and Mais<sup>5</sup> had encountered the impure fifth bromoketone in a bromination of the enol benzoate of 1-decalone with N-bromosuccinimide in an aqueous medium. In connection with recent studies<sup>2,22</sup> on the stereochemistry of the kinetically controlled bromination process, we had noted that enol acetates in anhydrous media offered the best route to  $\alpha$ -bromo ketones and we felt that the two required bromo ketones XI and XII might be accessible if the enol acetate XIII could be prepared. Consequently, *cis*-1-decalone (V) was transformed into its enol acetate by treatment with isopropenyl acetate, a reagent which has sometimes been found<sup>23</sup> to afford the product of kinetic (or steric) rather than of thermodynamic control. These conditions were selected since we assumed that the undesired  $\Delta^{1(9)}$ -enol acetate XIV would result from enol acetylation under thermodynamically controlled conditions. The resulting enol acetate was a mixture whose composition could, however, be determined easily by nuclear magnetic resonance spectroscopy,<sup>24</sup> since only the  $\Delta'$ -enol acetate (*e.g.*, XIII) possesses an olefinic proton. A proton count by electronic integration showed that the enol acetate mixture consisted of 52%  $\Delta^1$ -(XIII) and 48%  $\Delta^{1(9)}$ -(XIV) enol acetate, thus suggesting that kinetically controlled bromination would yield some of the desired 2-bromo-*cis*-1-decalone (XI and/or XII). For the bromination, we selected

(22) C. Djerassi, N. Finch, R. C. Cookson and C. W. Bird, *THIS JOURNAL*, **82**, 5488 (1960).

(23) R. B. Moffett and D. I. Weisblat, *ibid.*, **74**, 2183 (1952); H. Vanderhaeghe, E. R. Katzenellenbogen, K. Dobriner and T. F. Gallagher, *ibid.*, **74**, 2810 (1952); E. H. Man, F. C. Frostick and C. R. Hauser, *ibid.*, **74**, 3228 (1952).

(24) We are grateful to Dr. J. N. Shoolery and Mr. L. Johnson of Varian Associates, Palo Alto, Calif., for these measurements.

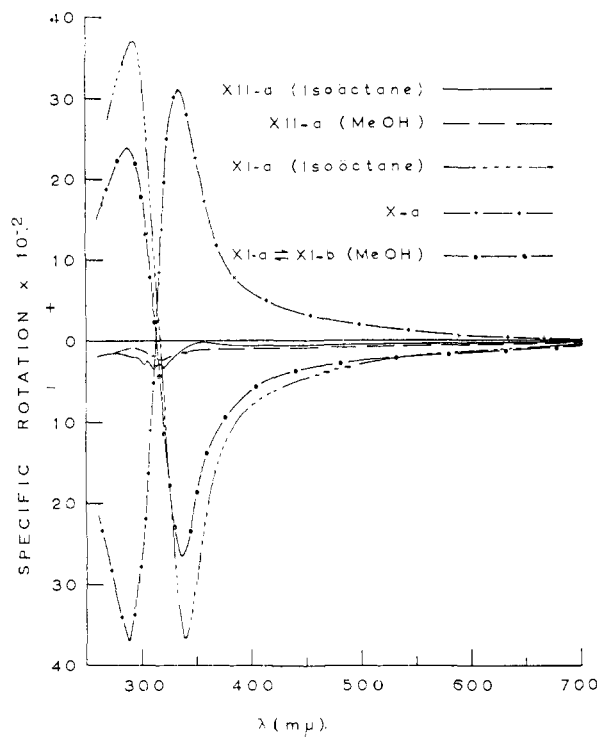


Fig. 2.—Optical rotatory dispersion curves (see footnote 16): (+)-9 $\alpha$ -bromo-*cis*-1-decalone (Xa) (methanol), (-)-2 $\alpha$ -bromo-*cis*-1-decalone (XI) (methanol as well as isoöctane) and (-)-2 $\beta$ -bromo-*cis*-1-decalone (XIIa) (methanol as well as isoöctane).

conditions (see Experimental) which in the steroid series<sup>25</sup> have been found to yield exclusively the kinetically controlled product. Chromatography on silica gel afforded five pure bromo ketones, of which three proved to be the earlier described<sup>5</sup> isomers VII, VIII and Xa. The remaining two were new and therefore had to represent the two missing isomers XI and XII. This was confirmed by debromination to *cis*-1-decalone (V), uncontaminated according to infrared assay by the *trans* isomer VI. Infrared and ultraviolet spectral measurements (Table I) indicated that one isomer contained an axial (XIa or XIIb) and the other an equatorial (XIb or XIIa) bromine atom. In order to differentiate among these possibilities, the optically active bromo ketones were prepared and their rotatory dispersion curves measured (Fig. 2).

As far as the two isomeric structures XIa and XIIb with an axial bromine atom are concerned, an immediate distinction is possible on the basis of the axial haloketone rule, which predicts a negative Cotton effect for XIa and a positive one for XIIb. As shown in Fig. 2 and Table I, the new bromo ketone with the axial bromine atom (as established by infrared and ultraviolet spectroscopy as well as by the bathochromic shift of the Cotton effect extrema) possesses a strong negative Cotton effect, whereupon we can conclude that this bromo ketone must possess structure XIa. Of particular interest is the question whether this conformer XIa exists in

(25) We are greatly indebted to Prof. E. R. H. Jones, Oxford University, for providing us with hitherto unpublished experimental details by M. Hartshorne and E. R. H. Jones.

mobile equilibrium with XIb upon changing the polarity of the solvent. Indeed as shown in Fig. 2, the rotatory dispersion Cotton effect of XI is considerably more negative in isoöctane (favoring axial halogen) than in methanol solution. There is no doubt, therefore, that *the existence of the conformational equilibrium XIa  $\rightleftharpoons$  XIb has been demonstrated.*

TABLE II  
CHARACTERISTIC INFRARED ABSORPTION BANDS<sup>a</sup>

$\lambda$ , $\mu$	1-Decalone		Bromodecalone					
	<i>cis</i> (V) <sup>b</sup>	<i>trans</i> (VI) <sup>b</sup>	Xa <sup>b</sup>	VIII <sup>b</sup>	IX <sup>c</sup>	VII <sup>b</sup>	XIa <sup>b</sup>	XIIa <sup>c</sup>
5.83	...	...	...	...	Max.	...	...	Max.
5.86	Max.	Max.	Max.	Max.	...	Max.	Max.	...
8.12	Max.	...	Max.	...	Min.	Min.	Max.	...
8.15	Max.	Min.	...	Max.	Max.	...	...	...
8.34	Max.	Max.	Min.	Min.	Min.	Max.	...	...
8.46	...	Min.	Min.	Min.	Min.	...	Max.	Min.
8.65	...	Min.	...	Max.	...	...	Min.	Min.
8.93	Min.	Min.	...	Max.	Min.	...	Max.	Min.
9.07	Max.	Max.	...	Max.	Min.	...	Min.	Min.
9.12	...	...	Max.	...	...	Max.	Max.	...
9.49	Max.	...	Max.	...	Max.	...	...	Max.
9.87	...	...	Min.	Max.	...	...	Min.	...
10.27	...	...	Max.	Min.	Min.	Min.	Max.	...
10.45	...	...	Min.	...	...	Max.	Min.	Min.
10.58	Max.	Min.	Max.	...	...	...	...	...
10.62	...	...	...	...	Min.	Min.	...	Max.
10.95	...	Min.	Min.	Max.	Max.	Min.	Min.	Min.
11.03	Min.	Max.	Min.	...	...	...	...	...
11.95	...	...	...	Max.	...	...	Max.	Max.
12.13	...	...	Max.	Max.	Min.	Max.	Min.	...
12.30	...	Max.	Min.	Max.	Min.	Min.	Min.	Min.
12.84	Max.	Min.	Min.	Min.	Max.	Max.	...	Max.
13.20	Min.	Min.	...	Max.	Min.	Min.	Min.	Min.
13.35	...	Min.	Max.	...	Min.	Min.	Min.	Min.
14.13	Min.	Min.	Min.	Min.	Max.	Min.	Min.	Max.
14.55	Min.	...	...	...	...	Max.	Max.	Max.

<sup>a</sup> In this table "Min." denotes either a minimum or a region of the spectrum devoid of absorption bands. The bands marked "Max." are of strong or medium intensity. <sup>b</sup> In a film. <sup>c</sup> In Nujol mull.

The next question then concerns itself with the quantitative aspects of this equilibrium. The amplitude of the Cotton effect in isoöctane is so similar to that of the pure axial bromo ketones VII, VIII and X that it can be concluded safely that in isoöctane we are dealing almost exclusively with the pure conformer XIa and its molecular rotation at the first extremum (trough) ( $\phi_{339} = -8265^\circ$ ) can, therefore, be used as a reference point for the pure conformer XIa. As far as pure XIb is concerned, no such value is available but a reasonable approximation can, nevertheless, be made. The axial haloketone rule states that equatorial halogen does not alter the sign of the Cotton effect of the parent ketone, although a small quantitative effect may be noted.<sup>26</sup> This contribution of the equatorial halogen can be calculated by comparing the rotations of the reference ketones *trans*-1-decalone (VI) and 2 $\alpha$ -bromo-*trans*-1-decalone (IX) at 339  $\mu$  and amounts to only  $\phi_{339} = +50^\circ$ . There remains to be determined the Cotton effect amplitude of the non-steroid form Vb of *cis*-1-decalone. By using the octant rule,<sup>27</sup> one can predict that the steroid conformation Va will exhibit a rather strong negative effect, while the "non-steroid" conformation Vb will show a weakly negative or possibly even posi-

(26) See p. 181 in ref. 8.

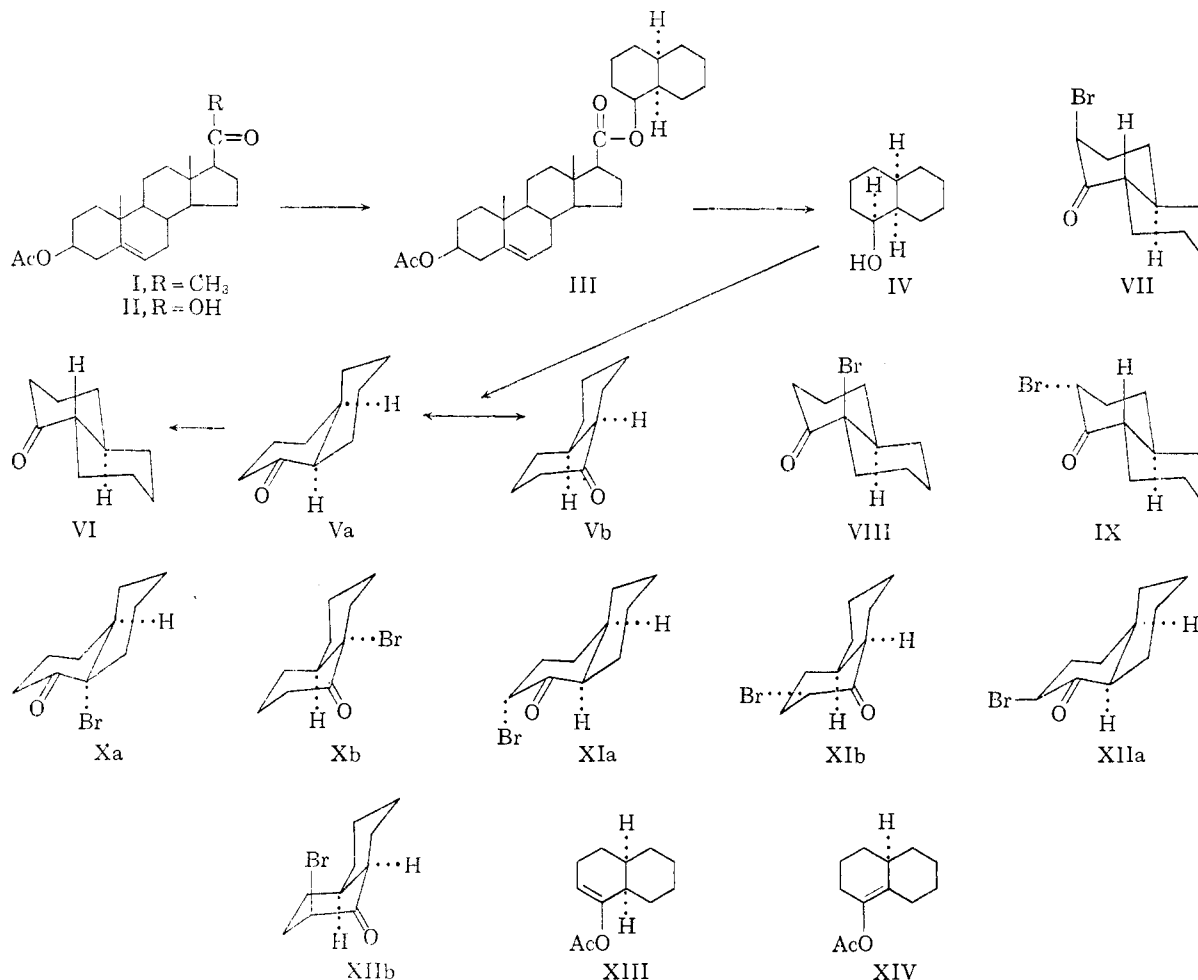
(27) See chapter 13 in ref. 8 as well as W. Klyne in R. A. Raphael, E. C. Taylor and H. Wynberg (eds.), "Advances in Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1960, pp. 333-341.

tive Cotton effect. The observed Cotton effect (Fig. 1 and Experimental, where data for fully resolved<sup>16</sup> ketone are listed) leads to the conclusion that *cis*-1-decalone exists predominantly in the "steroid" conformation Va, but it does not exclude the presence of substantial amounts of Vb. If we use  $\phi_{339} = -390^\circ$  derived from (-)-*cis*-1-decalone of Fig. 1 and add to it the above derived value of  $+50^\circ$  as the bromine contribution, we arrive at  $\phi_{339} = -340^\circ$  as one extreme value for XIb. If we now combine this with the value of  $\phi_{339} = -8265^\circ$  for pure XIa, we can calculate that in methanol solution, the equilibrium between XIa and XIb lies to the extent of 30% on the side of the equatorial conformer XIb. This value is a rather realistic one since even if we go to the extreme of supposing that pure XIb should actually possess a positive Cotton effect (assuming that pure Vb should be positive rather than weakly negative), the octant rule<sup>27</sup> definitely requires that it be less positive than (+)-2 $\alpha$ -bromo-*trans*-1-decalone (IX). Even if we take  $\phi_{339} = +280^\circ$  as an extreme value for pure XIb derived from Fig. 1 (IX), calculation still yields an equilibrium mixture of 72% XIa and 28% XIb in methanol solution.

We can now turn to the sixth and remaining pure bromo ketone, where spectral measurements have shown the bromine atom to exist in the equatorial conformation. Since conformation XIb is already excluded from the above rotatory dispersion studies, there remains only XIIa. Its rotatory dispersion curve in methanolic solution (where the equatorial form XIIa should be especially favored) is characterized (Fig. 2) by a negative Cotton effect, whose amplitude is much smaller than that of (-)-*cis*-1-decalone (V) itself. Since the amplitude of the latter's Cotton effect represents only a *minimum* value for XIIa (the equatorial halogen atom should actually make an additional small negative contribution) we can conclude that the equatorial (-)-2 $\beta$ -bromo-*cis*-1-decalone (XIIa) *must exist to a considerable extent in a non-chair form.*<sup>28</sup> The corresponding curve (Fig. 2) in the non-polar medium isoöctane does show the presence of a small quantity of another conformer (XIIb?) with a positive Cotton effect, but no quantitative calculations are possible since there are not available any rotational reference points for the pure conformers.

In summary, the above rotatory dispersion study of the six optically active monobromo-1-decalones has demonstrated that information can be deduced from rotatory dispersion, which would be accessible only with difficulty or not at all by any other physical method. Indeed, aside from the rotatory dispersion curve, only one additional piece of information is required (does a given bromo ketone upon debromination give a pure (*cis* or *trans*) 1-decalone or a mixture of *cis*- and *trans*-1-decalones?) to settle unambiguously the structures of the six possible isomeric  $\alpha$ -bromo-1-decalones. Consequently, if

(28) Any distortion of the chair form XIIa towards a boat (flexible form) will make the bromine atom more axial and at the same time create a tendency towards a positive rotation. Furthermore, it should be noted (see Table I) that the first extremum occurs at a wave length, which is intermediate between that of an equatorial (IX) and an axial (VII, VIII, etc.) bromine atom.



optically active material is available, the present approach is by far the easiest. However, other methods obviously can be used to this end, notably when working with racemates, and the studies of Zimmerman and Mais<sup>5</sup> represent an excellent example.

### Experimental<sup>29</sup>

**Conversion of Pregnenolone Acetate (I) to 3β-Acetoxy-Δ<sup>5</sup>-etiolic Acid (II).**—Bromine (28.8 g.) was added slowly to a vigorously stirred solution of 21 g. of sodium hydroxide in 180 cc. of water while cooling in an ice-salt-bath. When all the bromine had dissolved, the mixture was diluted with 120 cc. of cold dioxane and the ice-cold hypobromite solution was added slowly to a stirred solution of 14.4 g. of Δ<sup>5</sup>-pregnen-3β-ol-20-one acetate (I)<sup>30</sup> in 560 cc. of dioxane and 160 cc. of water which was maintained at a temperature below 8° throughout the oxidation. The homogeneous yellow solution slowly became colorless and a white precipitate formed. After 6 hr., the remaining oxidizing agent was destroyed by the addition of excess sodium sulfite solution and the mixture was then heated under reflux until the solid material dissolved. Acidification of the hot solution with concd. hydrochloric acid furnished a white precipitate of 3β-hydroxy-Δ<sup>5</sup>-etiolic acid, which was collected, washed with water and dried; yield 11.5 g., m.p. 272–274°.<sup>31</sup>

(29) Melting points were determined on the Kofler block. We are indebted to Mrs. T. Nakano for the rotatory dispersion measurements, to Miss B. Bach for the ultraviolet and infrared spectra and to Dr. A. Bernhardt (Mülheim, Germany) for the microanalyses.

(30) Grateful acknowledgment is made to Syntex, S.A., Mexico City, for this material.

(31) R. E. Marker and R. B. Wagner, *THIS JOURNAL*, **64**, 1842 (1942), have carried out this oxidation in approximately 10% yield by means of potassium hypoiodite.

A suspension of 11.5 g. of the hydroxy acid in 30 cc. of pyridine was left overnight at room temperature with 10 cc. of acetic anhydride, water (10 cc.) was added and the mixture heated under reflux until solution was complete. More water was added to incipient turbidity and, upon cooling, the desired 3β-acetoxy-Δ<sup>5</sup>-etiolic acid (II) separated as white plates. These were filtered, washed successively with dilute hydrochloric acid and water and finally dried at 105° (20 mm.), yield 11.5 g., m.p. 238–240°. This material was satisfactory for resolution work and gave no depression upon admixture with an authentic specimen (m.p. 246°)<sup>32</sup> of the acid.

**(-)-*cis,cis*-1-Decalol 3β-Acetoxy-Δ<sup>5</sup>-etiolate (III).**—A solution of 28.8 g. of 3β-acetoxy-Δ<sup>5</sup>-etiolic acid (II) in 100 cc. of thionyl chloride was stirred at room temperature for 4 hr. and the excess reagent was removed on the steam-bath *in vacuo*. The pale yellow crystalline acid chloride was dissolved in 100 cc. of pyridine (freshly distilled from barium oxide), cooled in ice, and an ice-cold solution of 12.4 g. of *cis,cis*-1-decalol (m.p. 91–92° obtained by hydrogenation of α-naphthol with platinum oxide in acetic acid<sup>4,15</sup>) in 25 cc. of pyridine was added. After stirring for 24 hr. at room temperature, the mixture was poured into ice-cold hydrochloric acid (380 cc. in 2 l. of water), the yellow precipitate was filtered, washed with dilute hydrochloric acid, water and air-dried. One recrystallization of the crude material (38 g.) from hexane afforded 25 g. of colorless needles of a mixture of diastereoisomers, m.p. 160–164°, [α]<sub>D</sub> -25.6° (chloroform). Three additional recrystallizations led to 9.5 g. of III, m.p. 175–177°, [α]<sub>D</sub> -32.5° (chloroform); material of this optical purity was used for all subsequent reactions.

(32) We are indebted to Dr. S. Szpilfogel (N. V. Organon, Oss, Holland) and Dr. A. Wettstein (Ciba Ltd., Basel, Switzerland) for generous samples of II, which were used in the first resolution experiments before the above-described oxidation of I to II had been developed.

Nine additional recrystallizations were required to give the optically pure diastereoisomer (3.0 g.), m.p. 183–183.5°,  $[\alpha]_D -36^\circ$  (chloroform). Neither the melting point or the rotation were altered by further recrystallization from hexane, acetone or methanol;  $\lambda_{\text{max}}^{\text{sol}} 5.80, 5.85, 8.01$  and  $8.05 \mu$ .

*Anal.* Calcd. for  $C_{20}H_{38}O_4$ : C, 77.37; H, 9.74. Found: C, 77.48; H, 9.64.

(-)-*cis,cis*-1-Decalol (IV).—The pure diastereoisomer III (1.65 g.) dissolved in 150 cc. of dry ether was reduced with 1.0 g. of lithium aluminum hydride in 100 cc. of ether (30 min., room temperature). After processing in the conventional manner (addition of ethyl acetate, followed by water and ether isolation), the desired decalol IV was extracted from the total solid by means of hexane. Evaporation of the solvent through a Vigreux column and sublimation gave 390 mg. of pure (-)-*cis,cis*-1-decalol (IV), m.p. 71–72°,  $[\alpha]_D -22^\circ$  (chloroform), whose infrared spectrum was completely superimposable upon that of the racemic decalol (m.p. 91–92°).

For larger scale work, 5 g. of the ester III of m.p. 175–177°,  $[\alpha]_D -32.5^\circ$ , was cleaved in a similar manner to afford 1.3 g. of (-)-*cis,cis*-1-decalol, m.p. 87–88° (with softening of 67°),  $[\alpha]_D -15.5^\circ$  (chloroform). This alcohol of 70% optical purity served as the starting material for further work.<sup>16</sup>

(-)-*cis*-1-Decalone (V).—A solution of 1.3 g. of (-)-*cis,cis*-1-decalol (IV),  $[\alpha]_D -15.5^\circ$ , in 50 cc. of glacial acetic acid was oxidized (5 hr., room temperature) with 0.6 g. of chromium trioxide in water. The resulting ketone was distilled at 45° (0.4 mm.) to afford 1.02 g. of (-)-*cis*-1-decalone,  $[\alpha]_D -51^\circ$  (chloroform), whose infrared spectrum (see Table II) was identical with that of the racemic ketone; R.D. (Fig. 1) in methanol (*c* 0.17):  $[\alpha]_{700} -27^\circ$ ,  $[\alpha]_{589} -39^\circ$ ,  $[\alpha]_{309} -657^\circ$ ,  $[\alpha]_{277.5} +278^\circ$ ,  $[\alpha]_{262.5} +209^\circ$ , R.D. in isoöctane (*c* 0.275):  $[\alpha]_{700} -41^\circ$ ,  $[\alpha]_{589} -57^\circ$ ,  $[\alpha]_{321} -627^\circ$ ,  $[\alpha]_{315} -528^\circ$ ,  $[\alpha]_{311} -597^\circ$ ,  $[\alpha]_{304-302} -305^\circ$  (infl.),  $[\alpha]_{277.5} +250^\circ$ ,  $[\alpha]_{255} +29^\circ$ .

Chromium trioxide oxidation of 100 mg. of optically pure (-)-*cis,cis*-1-decalol ( $[\alpha]_D -22^\circ$ ) afforded after distillation 60 mg. of optically pure (-)-*cis*-1-decalone; R.D. in methanol (*c* 0.18):  $[\alpha]_{700} -45^\circ$ ,  $[\alpha]_{589} -50^\circ$ ,  $[\alpha]_{309} -1070^\circ$ ,  $[\alpha]_{275} +470^\circ$ ,  $[\alpha]_{262} +310^\circ$ ; R.D. in isoöctane (*c* 0.155):  $[\alpha]_{700} -26^\circ$ ,  $[\alpha]_{589} -33.5^\circ$ ,  $[\alpha]_{322.5} -1116^\circ$ ,  $[\alpha]_{317.5} -942^\circ$ ,  $[\alpha]_{312.5} -1050^\circ$ ,  $[\alpha]_{277.5} +503^\circ$ ,  $[\alpha]_{262.5} +5^\circ$ .

(-)-*trans*-1-Decalone (VI).—A solution of 125 mg. of (-)-*cis*-1-decalone (V) ( $[\alpha]_D -51^\circ$ )<sup>15</sup> in 5 cc. of methanol containing one drop of concd. sulfuric acid was heated under reflux for 2 hr., poured into water, extracted with ether and finally distilled at 40° (0.1 mm.). The resulting (-)-*trans*-1-decalone (VI)<sup>16</sup> (109 mg.) was obtained as a colorless oil, whose infrared bands are listed in Table II. Of particular significance is the peak at 11.03  $\mu$ , absent in *cis*-1-decalone (V), and the absence of the latter's typical band at 10.58  $\mu$ ; R.D. (Fig. 1) in methanol (*c* 0.445):  $[\alpha]_{700} -18^\circ$ ,  $[\alpha]_{589} -22^\circ$ ,  $[\alpha]_{309} +705^\circ$ ,  $[\alpha]_{267.5} -1130^\circ$ ,  $[\alpha]_{251} -1083^\circ$ ; R.D. in isoöctane (*c* 0.16):  $[\alpha]_{700} -5^\circ$ ,  $[\alpha]_{589} -7^\circ$ ,  $[\alpha]_{320} +600^\circ$ ,  $[\alpha]_{315} +392^\circ$ ,  $[\alpha]_{311} +486^\circ$ ,  $[\alpha]_{272.5} -755^\circ$ ,  $[\alpha]_{260} -643^\circ$ .

Bromination of (-)-*cis*-1-Decalone (V).<sup>16</sup>—(-)-*cis*-1-Decalone ( $[\alpha]_D -51^\circ$ )<sup>16</sup> (1.0 g.) was dissolved in 25 cc. of acetic acid containing one drop of acetic acid saturated with hydrogen bromide. A solution of 1.04 g. of bromine and 0.55 g. of fused sodium acetate in 25 cc. of acetic acid was added dropwise over a period of 15 min. with stirring so that the rate of addition did not exceed the rate of bromine uptake. The mixture was then poured into water, extracted with ether-hexane (1:1), washed with water, dried and evaporated to leave the mixture of bromo ketones as a pale yellow oil (1.53 g.). These were separated by chromatography on 100 g. of silica gel,<sup>35</sup> the bromo ketone mixture being placed on the column with 40 cc. of hexane and elution being effected with hexane containing 2% of ether. The first 300 cc. of eluate contained negligible material and the bromo ketones started to be eluted shortly thereafter (al-

ways using the same solvent mixture); they were collected in twenty-five 20-cc. fractions, the composition of each fraction being determined by the infrared spectrum (Table II).

The first fraction afforded 108 mg. of (+)-9- $\alpha$ -bromo-*cis*-1-decalone (Xa), which was distilled at 40° (0.1 mm.). The substance crystallized at 0°, but melted below room temperature. Its infrared spectrum (Table II) was identical with that of the racemic ketone (m.p. 41.5–42.5°) prepared according to the literature directions<sup>3</sup>; R.D. (Fig. 2) in methanol (*c* 0.11):  $[\alpha]_{700} +25^\circ$ ,  $[\alpha]_{589} +50^\circ$ ,  $[\alpha]_{332} +3100^\circ$ ,  $[\alpha]_{288} -3700^\circ$ ,  $[\alpha]_{260} -2150^\circ$ ; R.D. in isoöctane (*c* 0.125):  $[\alpha]_{700} +75^\circ$ ,  $[\alpha]_{589} +100^\circ$ ,  $[\alpha]_{332} +3120^\circ$ ,  $[\alpha]_{288} -3650^\circ$ ,  $[\alpha]_{267} -2800^\circ$ .

Fractions 2–7 gave a mixture of Xa and VII, while fraction 8 led to 59 mg. of pure (+)-2- $\beta$ -bromo-*trans*-1-decalone (VII) as a low melting solid, which liquefied at room temperature. The relevant ultraviolet and infrared spectral properties are listed in Tables I and II; R.D. (Fig. 1) in methanol (*c* 0.10):  $[\alpha]_{700} +50^\circ$ ,  $[\alpha]_{589} +75^\circ$ ,  $[\alpha]_{330} +2850^\circ$ ,  $[\alpha]_{355} -3100^\circ$ ,  $[\alpha]_{260} -2100^\circ$ .

Fractions 9 and 10 contained VII contaminated with VIII. Infrared analysis of the combined fractions 11–14 (190 mg.) still indicated the presence of small amounts of VII and the 190 mg. was, therefore, rechromatographed on 30 g. of silica gel and finally distilled at 40° (0.1 mm.) to yield 40 mg. of (-)-9- $\beta$ -bromo-*trans*-1-decalone (VIII). The optically active ketone crystallized at 0°, but melted below room temperature; its infrared spectrum was identical with that of the racemic<sup>5</sup> bromo ketone VIII (m.p. 39–40°); R.D. (Fig. 1) in methanol (*c* 0.105):  $[\alpha]_{700} -100^\circ$ ,  $[\alpha]_{589} -150^\circ$ ,  $[\alpha]_{328} -2900^\circ$ ,  $[\alpha]_{285} +3700^\circ$ ,  $[\alpha]_{277.5} +3100^\circ$ ; R.D. in isoöctane (*c* 0.108):  $[\alpha]_{700} -100^\circ$ ,  $[\alpha]_{589} -125^\circ$ ,  $[\alpha]_{330} -3000^\circ$ ,  $[\alpha]_{285} +3850^\circ$ ,  $[\alpha]_{267.5} +2800^\circ$ .

Fractions 24 and 25 yielded 23 mg. of pure (+)-2- $\alpha$ -bromo-*trans*-1-decalone (IX), m.p. 105–106° (after sublimation at 90° (0.1 mm.) and an additional 60 mg. after rechromatographing fractions 15–23 (which contained a mixture of VIII and IX). The infrared spectrum (Table II) was identical with that of the racemic<sup>5</sup> ketone, m.p. 95–96°; R.D. (Fig. 1) in methanol (*c* 0.10):  $[\alpha]_{700} +15^\circ$ ,  $[\alpha]_{589} +20^\circ$ ,  $[\alpha]_{368} +500^\circ$ ,  $[\alpha]_{272} -850^\circ$ ,  $[\alpha]_{260} -710^\circ$ ; R.D. in isoöctane (*c* 0.10):  $[\alpha]_{700} +4^\circ$ ,  $[\alpha]_{589} +4^\circ$ ,  $[\alpha]_{315} +635^\circ$ ,  $[\alpha]_{310} +460^\circ$ ,  $[\alpha]_{307} +480^\circ$ ,  $[\alpha]_{270} -840^\circ$ ,  $[\alpha]_{260} -773^\circ$ .

Bromination of the Enol Acetate (XIII + XIV) of 1-Decalone.—A solution of 1.0 g. of racemic *cis*-1-decalone in 30 cc. of isopropenyl acetate containing 0.1 g. of *p*-toluenesulfonic acid was heated under reflux for 12 hr., when the solvent was distilled through a Vigreux column until the b.p. of the distillate reached 96°. The solution was heated for a further 6 hr., concentrated to 15 cc., diluted with ether and washed with dilute carbonate solution followed by water. Evaporation of the ether and isopropenyl acetate at 100° (20 mm.) left an oil which was distilled at 65–70° (0.07 mm.) to give 0.97 g. of the enol acetate mixture XIII + XIV;  $\lambda_{\text{max}}^{\text{sol}}$  5.72(s), 5.95(w), 8.15–8.25(s)  $\mu$ ; other characteristic strong bands appeared at 6.91, 7.31, 8.70, 8.89, 9.10, 9.40, 9.76, 9.88 and 10.95  $\mu$ . As indicated in the discussion, the n.m.r. spectrum demonstrated the presence of 52% of the  $\Delta^1$ - (XIII) and 48% of the  $\Delta^1$ (<sup>9</sup>)- (XIV) isomers.

*Anal.* Calcd. for  $C_{17}H_{18}O_2$ : C, 74.19; H, 9.34. Found: C, 73.97; H, 9.12.

A solution of 0.9 g. of bromine in 10 cc. of carbon tetrachloride was added slowly to an ice-cold, stirred solution of 0.97 g. of the above enol acetate in 10 cc. of carbon tetrachloride containing 0.6 g. of epichlorohydrin.<sup>25</sup> After 5 min., the solution was washed with dilute sodium sulfite solution and water, dried and evaporated. The resulting 1.41 g. of yellowish oil was chromatographed on a column of 100 g. of silica gel<sup>35</sup> exactly as described above, forty-three 15-cc. fractions being collected. The contents of fraction 2–3 were combined and recrystallized from hexane to yield 80 mg. of colorless needles, m.p. 38–39°. The optically active<sup>16</sup> antipode of this substance, (-)-2- $\alpha$ -bromo-*cis*-1-decalone (XIa), was obtained as a colorless oil when prepared from (-)-*cis*-1-decalone of  $[\alpha]_D -51^\circ$ . Its identity was established by infrared comparison (Table II) with the racemic bromo ketone; R.D. (Fig. 2) in isoöctane (*c* 0.405):  $[\alpha]_{700} -124^\circ$ ,  $[\alpha]_{589} -198^\circ$ ,  $[\alpha]_{330} -3670^\circ$ ,  $[\alpha]_{292.5} +3719^\circ$ ,  $[\alpha]_{280} +2330^\circ$ ; R.D. (Fig. 2) in methanol (*c* 0.40):  $[\alpha]_{700} -100^\circ$ ,  $[\alpha]_{589} -175^\circ$ ,  $[\alpha]_{335} -2650^\circ$ ,  $[\alpha]_{287.5} +2400^\circ$ ,  $[\alpha]_{260} +1500^\circ$ .

(33) The adsorbent was prepared by suspending 1 kg. of Mallinckrodt silicic acid (100 mesh) in 5 l. of water and allowing the mixture to settle for 5 min. The suspension of fine powder was then decanted from the sediment of coarser particles. The silica gel was free of dust after five such treatments and possessed more uniform sedimentation properties than the original material. It was filtered, washed with water, activated by heating at 120° for 24 hr., and then slightly deactivated by adding 5% by weight of distilled water and shaking for 4 hr.

*Anal.* Calcd. for C<sub>10</sub>H<sub>15</sub>BrO: C, 51.96; H, 6.54; Br, 34.55. Found: C, 52.03; H, 6.84; Br, 33.80.

Bromo ketones Xa, VII and VIII were eluted in fractions 5-35, while from fractions 35-43 there was isolated 80 mg. of a new bromo ketone, which exhibited m.p. 85.5-86.5° after recrystallization from iso-octane and sublimation at 60° (0.001 mm.). The optically active form,<sup>18</sup> (-)-2β-bromo-*cis*-1-decalone (XIIa), possessed m.p. 74-75° (softening at 65°) and an infrared spectrum (Table II) which was indistinguishable from that of the racemic ketone; R.D. (Fig. 2) in iso-octane (*c* 0.155): [α]<sub>100</sub> -18°, [α]<sub>589</sub> -26°, [α]<sub>586</sub> -50°, [α]<sub>555</sub> -20°, [α]<sub>320</sub> -304°, [α]<sub>316</sub> -285°, [α]<sub>311</sub> -337°.

[α]<sub>305</sub> -25°, [α]<sub>302.5</sub> -273°, [α]<sub>292.5</sub> -260° (inflect.), [α]<sub>275</sub> -150°, [α]<sub>260</sub> -197°; R.D. (Fig. 2) in methanol (*c* 0.175): [α]<sub>700</sub> -48°, [α]<sub>589</sub> -55°, [α]<sub>319</sub> -234°, [α]<sub>294</sub> -94°, [α]<sub>265</sub> -155°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>15</sub>BrO: C, 51.96; H, 6.54. Found: C, 51.84; H, 6.28.

Debromination of either racemic XI or racemic XII (30 mg.) with 200 mg. of zinc and 3 cc. of acetic acid (4 hr., room temperature) and extraction with ether provided 12 mg. of *cis*-1-decalone, whose infrared spectrum (notably absence of 11.03 μ band—see Table II) showed the absence of significant amounts of *trans*-1-decalone.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE INSTITUTE OF TECHNOLOGY, CLEVELAND 6, OHIO]

## Aromatic Amination with Alkylhydroxylamines<sup>1,2</sup>

BY PETER KOVACIC AND J. LINDSLEY FOOTE<sup>3</sup>

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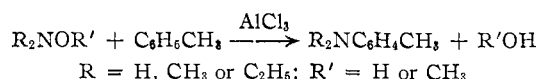
Various alkylhydroxylamines were investigated as aminating agents in the toluene-aluminum chloride system. The yields of aromatic amine decrease with increasing alkyl substitution on nitrogen. The orientation of substitution is predominantly *ortho-para* with a relatively high percentage *meta*. The mechanism of the reaction is discussed in terms of aromatic substitution by an electrophilic species of considerable activity.

### Introduction

A brief survey of direct aromatic amination has been presented in a previous paper.<sup>4</sup> The most pertinent examples in connection with the present work are the aminations with hydroxylammonium salts<sup>5,6</sup> and hydroxylamine-O-sulfonic acid.<sup>4,7,8</sup> The objectives of the present study were to effect aromatic amination with alkylhydroxylamines and determine the mechanism of this reaction.

### Results and Discussion

O-Methyl-, O,N-dimethyl-, O,N,N-trimethyl-, N,N-diethylhydroxylamine and hydroxylamine were investigated as aminating agents in the toluene-aluminum chloride system. The amination reaction is illustrated by the equation

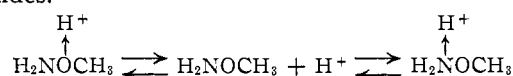


The reaction mixtures were heated at 100-111° for 10-60 minutes. In order to reduce the possibility of diamination, a tenfold molar excess of the aromatic compound was used. It was found that a twentyfold excess of toluene gave essentially the same results. Since amination with hydroxylamine-O-sulfonic acid is known<sup>9</sup> to proceed best with two molar equivalents of aluminum chloride per mole of aminating agent, the same ratio was used in this

study. Isomer distributions were determined by infrared analysis of the purified amines.

The amination reactions displayed the following characteristics: predominant *ortho-para* orientation, relatively low *ortho-para* ratio, relatively high *meta* orientation, catalysis by aluminum chloride, and yield of aminated product related to the structure of the alkylhydroxylamine as: O-methyl- > O,N-dimethyl- > O,N,N-trimethyl-, N,N-diethyl- (Table I).

It is likely that an alkylhydroxylamine-catalyst complex is involved in the transition state. The actual catalyst might be either aluminum chloride or a proton<sup>10</sup> (for the sake of simplicity, the proton will be used to designate the catalyst). Since there are two basic sites (nitrogen and oxygen) in the hydroxylamine compounds capable of coordination with the catalyst, the situation is more complex than in aromatic substitution with alcohols or alkyl halides.



By analogy with the Friedel-Crafts reaction and since it is improbable that amination would be

affected by the ammonium species, the H<sub>2</sub>NOCH<sub>3</sub> complex is presumed to be the attacking reagent. With a Lewis acid catalyst coordinated on oxygen, the oxygen-nitrogen bond would be polarized so as to increase the cationic character of the nitrogen.

Those alkylhydroxylamines possessing an O-methyl group would also be expected to alkylate toluene, perhaps as the initial preferred reaction. Indeed, xylene was isolated as a reaction product, although it is not known to what extent disproportionation of toluene was involved. Formation of benzene, xylene and mesitylene in the hydroxylamine reaction definitely shows that disproportiona-

(10) G. F. Hennion and R. A. Kurtz, *J. Am. Chem. Soc.*, **65**, 1001 (1943).

(1) Part II of a series on "Direct Aromatic Amination."

(2) Taken in part from the Ph.D. thesis of J. L. Foote, Case Institute of Technology, 1960. This paper was presented at the 137th Meeting of the American Chemical Society in Cleveland, Ohio, April, 1960, Abstracts of Papers, p. 56-O.

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(7) R. N. Keller and P. A. S. Smith, *J. Am. Chem. Soc.*, **68**, 899 (1946).

(8) R. N. Keller and P. A. S. Smith, *ibid.*, **66**, 1122 (1944).

(9) P. A. S. Smith, Doctoral Dissertation, University of Michigan, 1944.