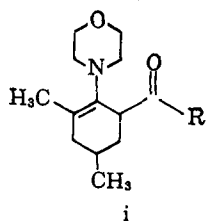


by chromic acid oxidation of cycloheximide itself. It appears that VI is almost the exclusive product of C-acylation.<sup>10,11</sup> Catalytic reduction of VI in acetic acid over platinum then afforded *dl*-dihydrocycloheximide (VII)<sup>12</sup> in 52% yield, m.p. 164–165°. *Anal.* Found: C, 63.3; H, 8.9; N, 4.9.

(10) In an article which appears to have been largely ignored [see, however, M. Kuehne, *J. Am. Chem. Soc.*, **81**, 5400 (1959)], W. R. N. Williamson [*Tetrahedron*, **3**, 314 (1958)] has suggested that the inability of alkyl halides to C-alkylate the enamines of 2-alkyl cyclohexanones was due in part to the steric effects of the 2-alkyl substituent. The latter, he postulated; assumed a quasi-axial position in the dipolar form of the enamine. The results of our synthetic work now seem to support these ideas, and it would appear that enamines of 2-alkylated cyclohexanones do indeed have the 2-alkyl group in a quasi-axial position. Thus, these materials present possibilities for accomplishing syntheses where an endergonic process is called for. Whereas the authors prefer the above argument, an alternative reason for appearance of *trans*-methyl groups in VI could be found if it is assumed that the product of acylation has the structure shown in i, and that the decomposition step is a kinetically controlled process and leads to the more unstable configuration for the 2-methyl group.



(11) After this work was completed, the synthesis of optically active dehydrocycloheximide was reported by H. J. Schaeffer and V. K. Jain [*J. Pharm. Sci.*, **52**, 509 (1963)], who used the optically active piperidine enamine derived from (+)-*trans*-2,4-dimethylcyclohexanone.

Thus, in two relatively simple steps we were able to establish *stereoselectively five asymmetric centers*, four of which were required in the final product.

The conversion of VII to I by partial oxidation proceeded with only a small yield, and the following procedure proved much more satisfactory.

Monoacylation of VII with chloroacetyl chloride<sup>13</sup> in dioxane-pyridine led to a 65% yield of VIII, m.p. 183–184° (*Anal.* Found: C, 56.5; H, 7.0; Cl, 10.2; N, 4.1), which on oxidation with chromium trioxide in aqueous acetone containing a little acetic acid afforded *dl*-cycloheximide chloroacetate (IX), m.p. 137–138° in good yield. *Anal.* Found: C, 56.8; H, 6.6; Cl, 10.2; N, 3.9.

Hydrolysis of IX with aqueous potassium bicarbonate than gave racemic cycloheximide (I), m.p. 139–140°, whose solution infrared spectrum and n.m.r. spectra in deuteriochloroform and pyridine were identical with those of the natural product. *Anal.* Found: C, 64.3; H, 8.1; N, 5.0.

When the above synthetic sequence was repeated using *cis-d*-2,4-dimethylcyclohexanone, *l*-cycloheximide, m.p. 114–115°, [ $\alpha$ ]<sub>D</sub><sup>25</sup> −33° (*c* 1.0, chloroform), was obtained. *Anal.* Found: C, 63.9; H, 8.2; N, 5.1. This was identical in all respects with the naturally occurring material.

This work represents a *total synthesis* of optically active I since *cis-dl*-II has been resolved previously.<sup>14</sup> In addition it formally represents a total synthesis of *d*-naramycin-B and a new synthesis of *d*-isocycloheximide,<sup>14,15</sup> since *l*-I has been isomerized to these two substances by Okuda, *et al.*<sup>16</sup>

A full paper dealing with this synthesis and the stereochemical problems involved will appear at a later date.

(12) Infrared evidence suggests that VI exists in the enolic form depicted! Thus, two conformers, VIa and VIb, present themselves for reduction, and Dreiding models suggest that VIb would be the one most easily reduced since it should present much less steric hindrance to the approach of the catalyst in the area of the molecule where reduction is taking place.

(13) Considerable difficulty was experienced in finding a protecting group for the side-chain hydroxylic group which would not be transferred easily to the ring hydroxyl by anchimeric assistance, but which could be subsequently hydrolyzed without destroying the acid- and base-sensitive aldehyde and glutarimide functions in I. The group in question filled these requirements.

(14) E. C. Kornfeld, R. G. Jones, and T. V. Parke, *J. Am. Chem. Soc.*, **71**, 150 (1949).

(15) A. J. Lemin and J. H. Ford, *J. Org. Chem.*, **25**, 344 (1960).

(16) T. Okuda, M. Suzuki, T. Furumai, and H. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **10**, 639 (1962).

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### Restricted Rotation in Aromatic Aldehydes

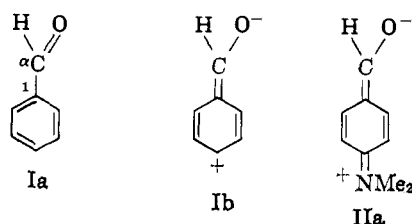
Sir:

The evidence<sup>1</sup> available suggests that benzaldehyde (I) is planar, presumably because of resonance interaction<sup>2</sup> of the type Ia ↔ Ib. This interaction should also give rise to an appreciable barrier to internal rotation about the C<sub>1</sub>C<sub>α</sub> bond; however, the magnitude

(1) E. A. Braude in E. A. Braude and F. C. Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, N. Y., 1955, p. 172; R. Bramley and R. J. W. LeFèvre, *J. Chem. Soc.*, 56 (1962).

(2) However, the resonance energies of benzene (36 kcal./mole) and of benzaldehyde (35 kcal./mole) obtained from combustion data are virtually the same [G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, pp. 99, 108]. Dispersion forces may also stabilize the planar form; cf. the calculations of W. T. Simpson, *J. Am. Chem. Soc.*, **73**, 5363 (1951), on butadiene; see also R. S. Mulliken, *Tetrahedron*, **6**, 68 (1959), and W. F. Yates, *J. Phys. Chem.*, **65**, 185 (1961).

of the barrier is not known. We have now found that low temperature n.m.r. spectra (60 Mc./sec.) of *p*-N,N-dimethylaminobenzaldehyde (II), *p*-methoxybenzaldehyde (anisaldehyde, III), and of I provide information on this point.



The aromatic protons of II and III gave rise to  $A_2B_2$  (approximately  $A_2X_2$ ) systems at room temperature,<sup>3</sup> but to much more complex spectra at low temperatures (*e.g.*, below about  $-85^\circ$  for II and  $-115^\circ$  for III). The main change was a splitting of the resonance signal of the protons *ortho* to the aldehyde group; little change was observed in the bands of other protons. Thus, at the low temperatures the *ortho* protons become nonequivalent, as is expected<sup>4</sup> if the rate constant for internal rotation becomes<sup>5</sup> much less than  $\pi\nu\sqrt{2}$ , where  $\nu$  (in c.p.s.) is the relative chemical shift between the nonequivalent protons.

With II, the situation was simplified by the use of 4-N,N-dimethylaminobenzaldehyde-3,5- $d_2$  (IIa) together with strong double-irradiation at the deuterium resonance frequency. The aromatic protons then gave a single sharp line at room temperature and an AB quartet ( $\nu_{AB} = 8.4$  c.p.s.,  $J = 2.5$  c.p.s.) below about  $-85^\circ$ .

TABLE I

Compound	Solvent	Coalescence temperature, $^\circ\text{C}$ .	$\Delta F^*$ , kcal./mole
Ph CHO (I)	Vinyl chloride	-123	7.9
 Me <sub>2</sub> N-CHO (IIa)	CH <sub>2</sub> Cl <sub>2</sub>	-71	10.8
 MeO-CHO (III)	Vinyl chloride	-99	9.2

Changes very similar to those occurring in the spectra of II and III took place below about  $-120^\circ$  in the spectrum of I. Measurements of the spectra of I, IIa, and III at intermediate temperatures gave apparent coalescence temperatures<sup>4,5</sup> (Table I) from which the free energies of activation ( $\Delta F^*$ ) for internal rotations were calculated<sup>6</sup> (Table I).

The increase ( $\Delta\Delta F^*$ ) in  $\Delta F^*$  of II over I may be ascribed to a direct resonance interaction of the aldehyde and dimethylamino groups (*i.e.*, to a contribution of IIa to the resonance hybrid of II). The energy of this interaction (2.8 kcal./mole) is a little greater, as expected, than that (2.5 kcal./mole) calculated by

(3) The room temperature spectra of I, II, and III are well known; see for example, N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "N.M.R. Spectra Catalog," Varian Associates, Palo Alto, Calif., 1961. The protons *ortho* to the aldehyde group in each case occur at lower field than the other aromatic protons.

(4) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Co., Inc., New York, N. Y., 1959.

(5) Because of the presence of coupling, this expression<sup>4</sup> is not strictly correct, but the error involved should be small.

(6) The values of  $\Delta F^*$  were calculated from the absolute rate theory for internal rotation over only one of the two possible barriers to rotation.

Taft<sup>7</sup> for the resonance interaction of a dimethylamino group and a *p*-carbomethoxy group.

It is planned to investigate the low temperature spectra of other aromatic aldehydes, and particularly of suitably deuterated derivatives, so as to obtain values of  $\Delta H^*$  and  $\Delta S^*$ . The present results, as far as they go, are in agreement with the finding, from ultrasonic measurements<sup>8</sup> of appreciable barriers (*ca.* 5 kcal./mole) in  $\alpha\beta$ -unsaturated aldehydes.

**Acknowledgments.**—This work was supported by the National Research Council of Canada.

(7) R. W. Taft, Jr., in M. S. Newman "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, p. 583.

(8) M. S. de Groot and J. Lamb, *Proc. Roy. Soc. (London)*, **A242**, 36 (1957).

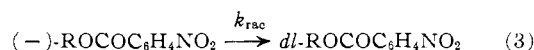
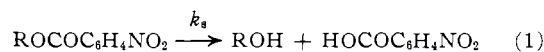
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RECEIVED NOVEMBER 9, 1963

### On the Nature of Ion-Pair Intermediates Involved in the Solvolysis of *p*-Chlorobenzhydryl *p*-Nitrobenzoate

We recently reported<sup>1</sup> that ion-pair return associated with solvolysis (alkyl-oxygen cleavage) of *p*-chlorobenzhydryl *p*-nitrobenzoate in aqueous acetone (reaction 1) results in randomization of the carboxyl oxygen atoms of  $^{18}\text{O}$ -labeled ester (reaction 2) and racemization of optically active substrate (reaction 3). These transformations are first order and the last two are intramolecular.<sup>1</sup> This shows that ion-pair return is cleanly isolated from external ion return<sup>2</sup> and thus the two transformations of the unsolvolyzed ester (reactions 2 and 3) result from ion-pair return.<sup>3</sup>



Assuming that ionization gives rise to an ion pair in which the carboxyl oxygen atoms are equivalent,<sup>1,4,5</sup> oxygen equilibration ( $k_{\text{eq}}$ ) measures total ion-pair return and  $k_{\text{rac}}$  measures racemization associated with this return. At  $100^\circ$  the  $k_{\text{eq}}/k_{\text{rac}}$  ratios for 80 and 90% acetone are 2.3 and 2.6, respectively. This shows that return involves predominating retention of configuration.

At the time of our earlier report<sup>1</sup> an important question concerning the stereochemical behavior of ion-pair species was left unanswered. This is whether the observed return is exclusively internal return (*i.e.*, one intermediate which returns with partial loss of configuration) or if external ion-pair return<sup>2</sup> is also involved (two intermediates). We now wish to report evidence that at least two distinct ion-pair species are involved. The evidence is as follows. In the presence of 0.14 *M* sodium azide, ion-pair return also occurs (the carboxyl oxygen atoms mix), however, in this case, the optical configuration of the unsolvolyzed ester is preserved fully, *i.e.*,  $k_{\text{rac}} = 0$ . Clearly, the nucleophilic azide ion is intercepting an intermediate that otherwise

(1) H. L. Goering, R. G. Briody, and J. F. Levy, *J. Am. Chem. Soc.*, **85**, 3059 (1963).

(2) S. Winstein, P. E. Klinedinst, Jr., and G. C. Robinson, *ibid.*, **83**, 885 (1961).

(3) The effects of varying structure and solvent on the rates and relative rates of reactions 1-3 are consistent with this interpretation (ref. 1 and 4).

(4) H. L. Goering and J. F. Levy, *J. Am. Chem. Soc.*, **84**, 3853 (1962).

(5) H. L. Goering and M. M. Pombo, *ibid.*, **82**, 2515 (1960); H. L. Goering and J. T. Doi, *ibid.*, **82**, 5850 (1960); H. L. Goering, M. M. Pombo, and K. D. McMichael, *ibid.*, **85**, 965 (1963).