

% excess  $N^{15}$  in this N atom of the pyrazine ring equals that of the sum of the two N atoms of the pyrazine ring, it is apparent that the other atom is similarly labeled.

It was determined directly as follows: the solution from the above reaction containing N-methyl-3,4-dimethyl aniline derived from 66 mg. of (X) was extracted well with ether, and the acidic aqueous phase was collected. The solution was made alkaline and again extracted with ether. Evaporation of the ether gave a brown oil which was suspended in dil. NaOH and steam distilled. The steam distillate containing (XIV) was treated with *p*-toluenesulfonyl chloride and NaOH solution. The crude *p*-toluenesulfonamide of

(XIV) separated, and it was washed well with dil. NaOH. The low-melting solid (40–60°) containing (XV) was crushed and analyzed for  $N^{15}$  without further purification.

1,5,6-Trimethylbenzimidazole.—15 mg. of (X) were refluxed with 5 ml. of 1 *N* HCl and 5 drops of HCOOH for 3 hrs.<sup>25</sup> The pH was adjusted to 8, and (XI) was taken up into  $CHCl_3$ . The residue was sublimed at 120°; 10 mg. were obtained, m.p. 139° (in a sealed tube). The m.p. reported for the authentic substance is 143–144°.<sup>2</sup>

(25) N. G. Brin and K. Folkers, *J. Am. Chem. Soc.*, **72**, 4442 (1950).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY, STANFORD, CALIF., AND THE INSTITUTE OF CHEMISTRY, UNIVERSITY OF UPPSALA, SWEDEN]

## Optical Rotatory Dispersion Studies. XLVIII.<sup>1</sup> The Nitroso Chromophore<sup>2</sup>

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Optically active nitroso compounds exhibit Cotton effects which can be related in terms of wave length to their  $\eta \rightarrow \pi^*$  absorption transition. The rather rare C-nitroso chromophore shows a Cotton effect in the visible centered around 675  $m\mu$ , while that of a N-nitrosodialkylamine occurs between 350–400  $m\mu$ . These single Cotton effects are in marked contrast to the multiple Cotton effect curves exhibited by N-nitrosoamides which are found in the region 450–300  $m\mu$ . The rotatory dispersion curves of a number of N-nitroso derivatives of N-acetyl- or N-benzoyl- $\alpha$ -amino acids have been investigated and their Cotton effects can be used for stereochemical assignments. N-Nitroso-N-methylamides of optically active carboxylic acids also show multiple Cotton effects, but these cannot always be employed for determining the absolute configuration of the  $\alpha$ -asymmetric center.

Initially, our studies on the role of optical rotatory dispersion measurements in organic chemistry<sup>4</sup> centered on the carbonyl chromophore. Once the utility of this physical method had been demonstrated for structural and especially stereochemical problems, we turned to an investigation<sup>5</sup> of "chromophoric" derivatives which afford Cotton effect curves for otherwise "nonchromophoric" functional groups (*e.g.*, hydroxyl, carboxyl, amino, etc.). Concurrent with this work, we have also undertaken a screening program of various chromophores—notably those with low intensity extinction coefficients—whose spectral properties would suggest that they might exhibit anomalous optical rotatory dispersion. As pointed out elsewhere,<sup>4,4</sup> it is this area of optical rotatory dispersion measurements which has by far the greatest scope in terms of applications to organic chemical problems. In this connection, we completed recently a survey of optically active disulfides and diselenides,<sup>6</sup> and we should now like to record our experience with the nitroso chromophore.

The recorded<sup>7</sup> maxima for the  $\eta \rightarrow \pi^*$  transition of the nitroso chromophore occur approximately

at 680  $m\mu$  for the C-nitroso function, 370  $m\mu$  for N-nitrosoamines and nitrites and at 415  $m\mu$  for N-nitrosoamides; if these bands should be optically active, then Cotton effects would be expected in these spectral regions. In fact, the only two earlier studies<sup>8,9</sup> show that this is so. Organic alkyl nitroso compounds are rather unavailable and this applies particularly to optically active ones. It is not surprising, therefore, that no rotatory dispersion studies have been recorded for the isolated C-nitroso chromophore, but Mitchell's measurements<sup>8</sup> of the circular dichroism of caryophyllene and bornylene nitrosites (nitroso nitrites) indicate that the 680  $m\mu$  transition is optically active. Through the kind cooperation of Prof. G. Büchi and Dr. F. W. Bachelor, we have been able to secure a specimen of the aconitine derivative I,<sup>10</sup> which represents a non-enolizable C-nitroso compound. Its single absorption band above 300  $m\mu$  occurs at 679  $m\mu$  ( $\epsilon$  14) and, as can be seen from Fig. 1, this gives rise to a negative Cotton effect.

While this result is principally of theoretical interest because of the inaccessibility of optically active tertiary C-nitroso compounds and is thus unlikely to be of any stereochemical utility, this is not necessarily the case with N-nitrosoamines. The rotatory dispersion behavior of such compounds has hitherto not been examined, but their comparative ease of preparation makes them of potential interest as "chromophoric" derivatives of optically active amines, since their low-intensity

Clarke, J. R. Johnson and R. Robinson), Princeton University Press, Princeton, N. J., 1949, pp. 144–206.

(8) S. Mitchell, *J. Chem. Soc.*, 3258 (1928); S. Mitchell and S. B. Carmack, *ibid.*, 415 (1932).

(9) W. Kuhn and H. L. Lehmann, *Z. physik. Chem.*, **B18**, 32 (1932); W. Kuhn and H. Biller, *ibid.*, **B29**, 1 (1935); H. B. Elkins and W. Kuhn, *J. Am. Chem. Soc.*, **57**, 296 (1935).

(10) F. W. Bachelor, R. F. C. Brown and G. Büchi, *Tetrahedron Letters*, No. 10, 1 (1960).

(1) Paper XLVII, C. Djerassi, *Tetrahedron*, in press (1961).

(2) Supported by Grant No. CRTC-5061 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

(3) National Institutes of Health Postdoctorate Research Fellow.

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

(5) (a) B. Sjöberg, A. Fredga and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 5002 (1959); (b) C. Djerassi and K. Undheim, *ibid.*, **82**, 5755 (1960); (c) E. Bunnenberg and C. Djerassi, *ibid.*, **82**, 5953 (1960); (d) C. Djerassi, K. Undheim, R. C. Sheppard, W. G. Terry and B. Sjöberg, *Acta Chem. Scand.*, in press (1961).

(6) C. Djerassi, A. Fredga and B. Sjöberg, *ibid.*, in press (1961).

(7) See J. W. Sidman, *Chem. Revs.*, **58**, 689 (1958); J. Mason, *J. Chem. Soc.*, 3904 (1957); R. N. Haszeldine and B. J. H. Mattinson, *ibid.*, 4172 (1955); R. N. Haszeldine and J. Jander, *ibid.*, 691 (1954); R. L. Peck and K. Folkers in "Chemistry of Penicillin" (ed. by H. T.

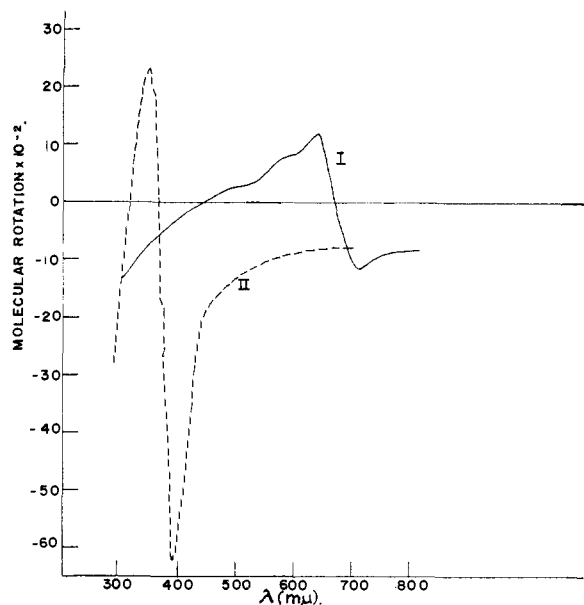


Fig. 1.—Optical rotatory dispersion curves of aconitine nitroso derivative I (methanol) and N-nitroso- $\alpha,\alpha'$ -dimethylbenzylamine (II) (dioxane).

absorption occurs<sup>7</sup> in a very convenient spectral region (near 370  $m\mu$ ). Recently, Overberger and collaborators<sup>11</sup> have synthesized N-nitroso- $\alpha,\alpha'$ -dimethyldibenzylamine (II) in optically active form. As shown in Fig. 1, its ultraviolet absorption band at 369  $m\mu$  gives rise to a single negative Cotton effect of very substantial amplitude and the preparation of other optically active N-nitrosoamines is clearly indicated in order to examine the feasibility of using their anomalous rotatory dispersion curves for absolute configurational assignments of optically active amines.

The single, most important classical experimental study of ultraviolet optical rotatory dispersion probably has been the work of Kuhn<sup>9</sup> with optically active nitrites. He showed that the fine structure in the ultraviolet absorption spectrum of alkyl nitrites is reflected in the corresponding circular dichroism curves and in the multiple Cotton effect of their respective rotatory dispersion curves. No further work has been done in this area, principally because of the reported<sup>12</sup> instability and difficulty in purification of such alkyl nitrites, and Kuhn's<sup>9</sup> results have proved to be largely of theoretical significance. The recent investigations by Barton and collaborators<sup>13</sup> on the photochemistry of steroidal nitrites indicate that crystalline nitrites frequently can be handled with ease and an examination of their rotatory dispersion behavior may prove profitable.

In the present instance, we have centered our attention on still another group of optically active nitroso derivatives, the nitrosoamides. Their chemis-

(11) C. G. Overberger, N. P. Marullo and R. G. Hiskey, *J. Am. Chem. Soc.*, **81**, 1517 (1959). We are indebted to Prof. Overberger for a specimen of his N-nitrosoamine II.

(12) K. Freudenberg and H. Biller, *Ann.*, **510**, 230 (1934); N. Kornblum and E. P. Oliveto, *J. Am. Chem. Soc.*, **69**, 465 (1947).

(13) D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *ibid.*, **82**, 2640 (1960); D. H. R. Barton and J. M. Beaton, *ibid.*, **82**, 2641 (1960); A. L. Nussbaum, F. E. Carlon, E. P. Oliveto, E. Townley, P. Kabasakalian and D. H. R. Barton, *ibid.*, **82**, 2973 (1960).

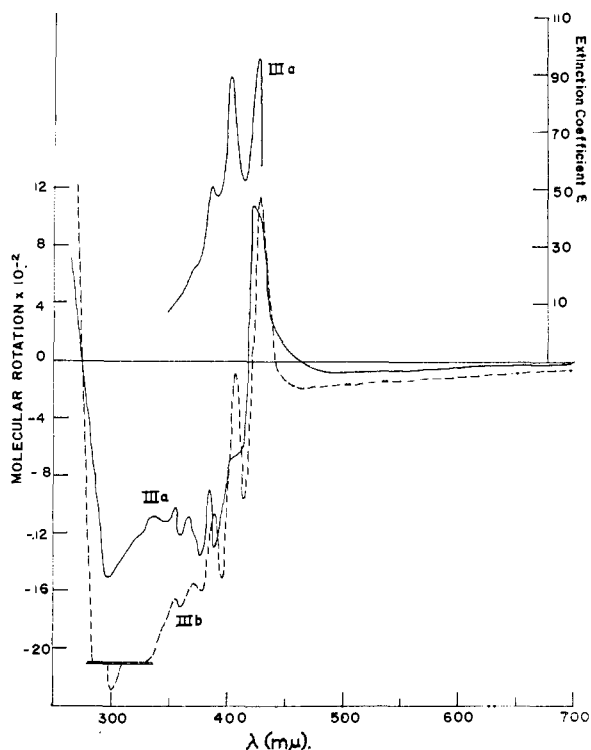


Fig. 2.—Optical rotatory dispersion curves (isoöctane) of N-nitroso-N-acetyl-L-leucine methyl ester (IIIa) and N-nitroso-N-benzoyl-L-leucine methyl ester (IIIb) as well as ultraviolet absorption spectrum of IIIa.

try has received renewed attention in recent years,<sup>14</sup> but no work has been done on their optical rotatory dispersion behavior. We decided to examine this chromophore in terms of a closely related series of optically active N-nitrosoamides in order to see whether any anomalous optical rotatory dispersion features could also be correlated with their absolute configuration. For this purpose, we selected the N-nitroso derivatives of N-acetyl- and N-benzoyl- $\alpha$ -amino acid esters (III), a group of compounds whose absolute configuration is known. All of them were prepared by treating the N-acyl- $\alpha$ -amino acid ester with nitrogen tetroxide<sup>14</sup> in carbon tetrachloride solution in the presence of sodium acetate. The majority of the compounds proved to be relatively unstable oils, which were best stored at low temperature prior to analytical and spectroscopic measurements. Aside from analytical results, the purity of the N-nitrosoamide could be determined conveniently by infrared measurements, as the amide band at 6.10  $\mu$  of the N-acyl- $\alpha$ -amino acid is shifted to 5.8 (N-acetyl-N-nitrosoamine)–5.9  $\mu$  (N-benzoyl-N-nitrosoamine), and by ultraviolet measurements. From our standpoint, these were the most important and they exhibited generally a series of four maxima and shoulders in the region 375–430  $m\mu$ , a characteristic feature rather reminiscent of the fine structure observed by Kuhn<sup>9</sup> between 330–375  $m\mu$  in the spectra of alkyl nitrites. As will be shown below, these absorption bands of the N-nitrosoamides—just as

(14) *Inter al.*, E. H. White, *ibid.*, **77**, 6008, 6011, 6014 (1955); K. Heyns and A. Heins, *Ann.*, **634**, 29 (1960), and references cited therein.

was the case with nitrites<sup>9</sup>—are all optically active and give rise to the multiple Cotton effects characteristic of this particular chromophore.

As a typical example we may consider N-nitroso-N-acetyl-(IIIa) and N-nitroso-N-benzoyl-(IIIb)-L-leucine methyl ester. Figure 2 contains the ultraviolet absorption spectrum as well as the optical rotatory dispersion curve of N-nitroso-N-acetyl-L-leucine methyl ester (IIIa) and it will be noted that there exists a Cotton effect corresponding to each absorption maximum or inflection. Some of the additional fine structure found in the rotatory dispersion curve could not be detected in the absorption spectrum and probably corresponds to very weak absorption bands which could not be measured. The rotatory dispersion curve of N-nitroso-N-benzoyl-L-leucine methyl ester (IIIb) is also reproduced in Fig. 2 and the general similarity between the two curves shows that the nature of the acyl substituent does not play an important role. The rotatory dispersion curves of N-nitroso-N-benzoyl-L-glutamic acid diethyl ester (IIIc) and of N-nitroso-N-benzoyl-O-acetyl-L-serine methyl ester (IIId) are shown in Fig. 3 in order to demonstrate their resemblance to the dispersion curves of the leucine derivatives of Fig. 2. The principal difference appears to be in the first extremum of the Cotton effect closest to the visible. If this is ignored, then it will be noted that the dispersion curves of all of the N-nitroso-N-acyl- $\alpha$ -amino acids of the L-series contained in Figs. 2 and 3, as well as those reported in the Experimental section (IIIe-IIIh), exhibit the characteristic feature of a series of Cotton effects of negative rotation value ending in a pronounced trough near 300 m $\mu$ . This rotatory dispersion characteristic is retained in the presence of a wide variety of substituents (IIIa-IIIh) and it seems safe to conclude that it could be used for purposes of establishing the absolute configuration of the asymmetric center to which the amino group is attached. For practical purposes, it is unlikely that this approach to absolute configurational studies in the  $\alpha$ -amino acid series will be used widely, since the alternate rotatory dispersion methods developed recently in our laboratories<sup>5a,5d</sup> utilize stable derivatives which are more conveniently prepared. Nevertheless, the above generalization appears to be of some potential use in that it should be amenable to extension beyond the  $\alpha$ -amino acid series. Thus, the rotatory dispersion curve (Fig. 3) of N-nitroso-N-acetyl-(+)-1,2,2-triphenylethylamine (IV)<sup>15</sup> is clearly of enantiomeric type from those of the L- $\alpha$ -amino acid derivatives, from which we conclude that stereoformula IV represents the correct absolute configurational representation of this substance. This in turn settles also the absolute configuration of the corresponding (+)-1,2,2-triphenylethanol with which IV has been related.<sup>16</sup>

In the above-described series of N-nitrosoamides, the nitrosoamine moiety was attached directly to the asymmetric center under discussion. It appeared of interest to see whether this grouping could also be utilized as a "chromophoric" deriva-

(15) See C. J. Collins, W. A. Bonner and C. T. Lester, *J. Am. Chem. Soc.*, **81**, 466 (1959). We are grateful to Dr. Collins for furnishing us with this material.

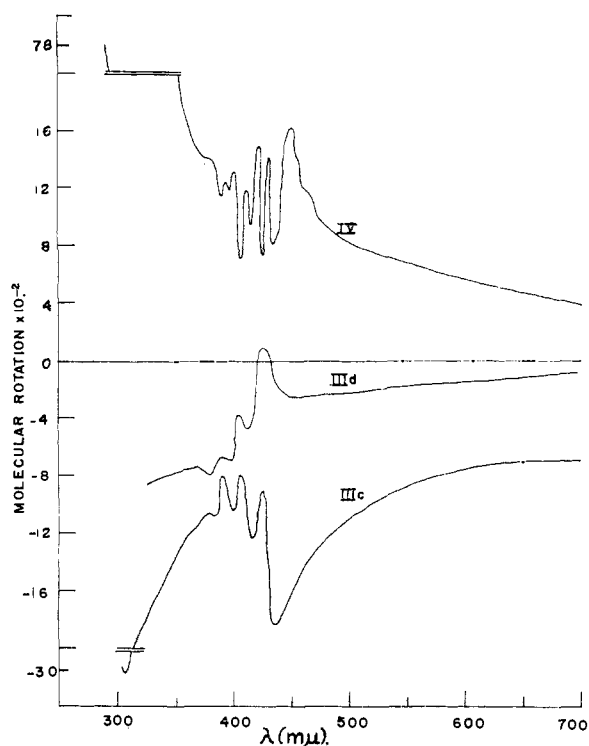


Fig. 3.—Optical rotatory dispersion curves of N-nitroso-N-benzoyl-L-glutamic acid diethyl ester (IIIc) (isoöctane), N-nitroso-N-benzoyl-O-acetyl-L-serine methyl ester (IIId) (dioxane) and N-nitroso-N-acetyl-(+)-1,2,2-triphenylethylamine (IV) (isoöctane).

tive for the carboxyl group since, *a priori*, it could not be predicted whether an anomalous dispersion curve would still be shown as the chromophore is removed further from the asymmetric center. As a model compound, we utilized the readily available (+)- $\alpha$ -methylbutyric acid, whose absolute configuration has been related<sup>16</sup> to L-glyceraldehyde. Attempts to prepare satisfactory N-nitroso derivatives of its anilide or 1,4-phenylenediamide failed, but N-nitroso-N-methyl- $\alpha$ -methylbutyramide (V) could be prepared readily although it could only be preserved at low temperature. Its ultraviolet absorption spectrum was practically identical with that of N-nitroso-N-acetyl-L-leucine (IIIa), reproduced in Fig. 2, and, most importantly, its rotatory dispersion curve was again characterized by a multiple Cotton effect (Fig. 4). Additional N-nitroso derivatives which were examined were prepared from the methyl amides of (-)- $\alpha$ -(2-naphthoxy)-propionic acid (VI),<sup>17</sup> (+)- $\alpha$ -phenylbutyric acid (VII)<sup>18</sup> and O-acetyl-D-lactic acid (VIII). Their rotatory dispersion curves are all collected in Fig. 4 and inspection will show that these cannot necessarily be employed for con-

(16) See J. A. Mills and W. Klyne in W. Klyne's "Progress in Stereochemistry," Academic Press, Inc., New York, N. Y., 1954, Vol. I, Chapter 5.

(17) The free acid and its amide exhibit plain dispersion curves (B. Sjöberg, *Arkiv. Kemi*, **15**, 451 (1960). For absolute configurational assignment by the quasiracemate procedure see A. Fredga and M. Matell, *ibid.*, **3**, 429 (1951)).

(18) For rotatory dispersion of acid and amide see A. Rothen and P. A. Levene, *J. Chem. Phys.*, **7**, 975 (1939), and B. Sjöberg, *Acta Chem. Scand.*, **14**, 273 (1960). E. Pettersson, *Arkiv. Kemi*, **10**, 283 (1956), discusses the absolute configuration of the acid.

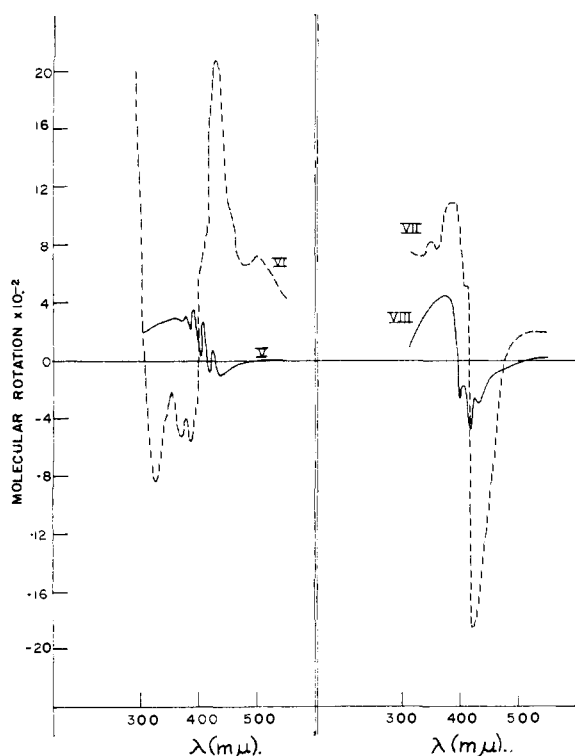


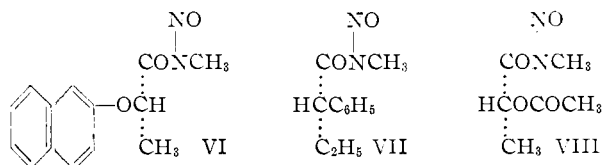
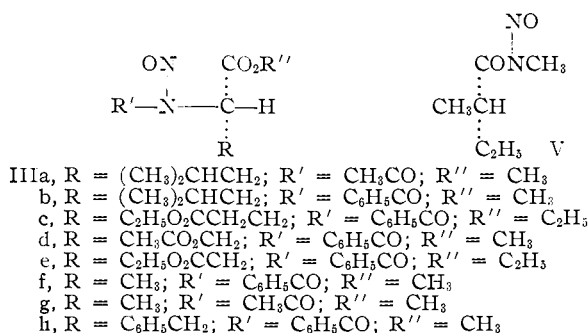
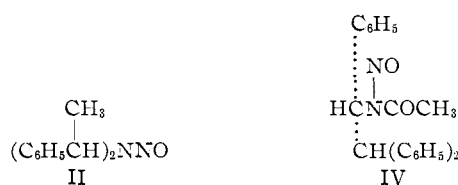
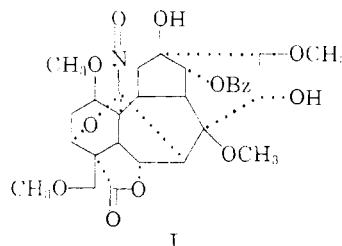
Fig. 4.—Optical rotatory dispersion curves of N-nitroso-N-methyl-(+)- $\alpha$ -methylbutyramide (V) (isoöctane), N-nitroso-N-methyl-(−)- $\alpha$ -(2-naphthoxy)-propionamide (VI) (dioxane), N-nitroso-N-methyl-(−)- $\alpha$ -phenylbutyramide (VII) (dioxane) and N-nitroso-N-methyl-O-acetyl-D-lactamide (VIII) (dioxane).

figural assignments. The curves of VII and VIII are similar in shape and sign, which is in agreement with their identical absolute configuration as is the antipodal character of the rotatory dispersion curve of VI, since the latter belongs to the opposite absolute configurational series compared with VII and VIII. The  $\alpha$ -methylbutyric acid derivative V, however, represents an anomaly and we believe that the following rationalization can account for this behavior.

The sign of the multiple Cotton effect associated with the nitroso chromophore is obviously affected by the spatial situation of the chromophore with respect to that of the other substituents. In theory, free rotation is possible around all of the single bonds in compounds V–VIII and it is difficult to assess the rotomer composition of this group of compounds. While in principle the same problem arises in the  $\alpha$ -amino acid derivatives III, the nitrosoamide grouping is attached directly to the asymmetric center and the only factor which has been varied is the nature of the  $\beta$ -substituent of the "R" group of III. Evidently, no major changes in the rotomer composition (using the nitroso group as reference point) have occurred in that group, thus leading to the observed coincidence of sign of multiple Cotton effect with absolute configuration.

The experimental survey of the nitroso chromophore recorded in this paper, coupled with Kuhn's earlier results<sup>9</sup> on nitrites, demonstrates that its

$\eta \rightarrow \pi^*$  transition is optically active, irrespective of the nature of the atom to which the chromophore is attached. The actual utility of rotatory dispersion measurements of optically active nitroso compounds for the solution of organic chemical problems will depend largely on their availability. The spectroscopic properties of the chromophore clearly make it a desirable candidate for more extensive investigation in the area of anomalous optical rotatory dispersion.



### Experimental<sup>19</sup>

**Nitrosation Procedure.**—White's<sup>14</sup> recommended procedure was employed in that a 5–10-fold excess of nitrogen tetroxide (Matheson) was collected in a suspension of 3 molar equivalents of anhydrous sodium acetate in dry carbon tetrachloride while cooling in a Dry Ice-acetone-bath. After warming to 0°, one molar equivalent of the amide was added and the mixture stirred for 15 min., poured into ice and the organic layer separated. The latter was washed with water, 5% sodium carbonate, again water, dried and then evaporated *in vacuo*, care being taken that all of the above operations were conducted at 0°. Solid products were recrystallized from ether-petroleum ether, while oils were dried in a high vacuum and then submitted directly to analysis and spectral measurements.

Aconitine nitroso derivative (I):  $^{10}\lambda_{\text{max}}^{\text{MeOH}}$  679 m $\mu$ ,  $\epsilon$  14; R.D. (Fig. 1) in methanol ( $c$  0.34):  $[\alpha]_{815} -140^\circ$ ,  $[\alpha]_{710}$

(19) We are indebted to Miss B. Bach for the infrared (unless noted otherwise, substances were deposited as a film) and ultraviolet absorption spectra and to Mrs. Ruth Records for the rotatory dispersion curves. The microanalyses were done in part by Mr. E. Meier (Stanford University Chemistry Department) and in part by the Berkeley Microanalytical Laboratory.

$-193^\circ$ ,  $[\alpha]_{670} 0^\circ$ ,  $[\alpha]_{640} +200^\circ$ ,  $[\alpha]_{610} +149^\circ$  (infl.),  $[\alpha]_{589} +130^\circ$ ,  $[\alpha]_{525} +51^\circ$  (infl.),  $[\alpha]_{300} -230^\circ$ .

**N-Nitroso- $\alpha,\alpha'$ -dimethyldibenzylamine (II)<sup>11</sup>.** R.D. (Fig. 1) in dioxane ( $c$  0.031):  $[\alpha]_{700} -316^\circ$ ,  $[\alpha]_{589} -361^\circ$ ,  $[\alpha]_{387.5} -2450^\circ$ ,  $[\alpha]_{372.5} -562^\circ$  (infl.),  $[\alpha]_{337.5} +742^\circ$  (infl.),  $[\alpha]_{350} +916^\circ$ ,  $[\alpha]_{290} -1100^\circ$ ;  $\lambda_{\max}^{\text{diox}} 369 \text{ m}\mu$ ,  $\epsilon 90$ .

**N-Nitroso-N-acetyl-L-leucine Methyl Ester (IIIa).**—Nitrosation of 60 mg. of N-acetyl-L-leucine methyl ester<sup>20</sup> ( $\lambda_{\max} 3.08, 5.79, 6.10 \mu$ ) afforded 49 mg. of oily N-nitroso-derivative IIIa,  $\lambda_{\max} 5.7-5.8 \mu$  (broad); ultraviolet in isoctane:  $\epsilon_{375}^{\text{shoulder}} 22$ ,  $\epsilon_{390}^{\text{max}} 51$ ,  $\epsilon_{392}^{\text{min}} 46$ ,  $\epsilon_{405}^{\text{max}} 89$ ,  $\epsilon_{415}^{\text{min}} 52$ ,  $\epsilon_{427}^{\text{max}} 95$ ; R.D. (Fig. 2) in isoctane ( $c$  0.150 to 295 m $\mu$ , then 0.006):  $[\alpha]_{700} 0^\circ$ ,  $[\alpha]_{589} -20^\circ$ ,  $[\alpha]_{500} -30^\circ$ ,  $[\alpha]_{425} +510^\circ$ ,  $[\alpha]_{410} -300^\circ$  (infl.),  $[\alpha]_{395} -600^\circ$ ,  $[\alpha]_{388} -410^\circ$ ,  $[\alpha]_{380} -630^\circ$ ,  $[\alpha]_{371} -500^\circ$ ,  $[\alpha]_{363} -565^\circ$ ,  $[\alpha]_{358} -475^\circ$ ,  $[\alpha]_{350} -520^\circ$ ,  $[\alpha]_{338} -500^\circ$ ,  $[\alpha]_{335} -528^\circ$ ,  $[\alpha]_{325} -570^\circ$ ,  $[\alpha]_{311} -643^\circ$ ,  $[\alpha]_{301} -705^\circ$ ,  $[\alpha]_{267} +330^\circ$ .

*Anal.* Calcd. for  $C_{16}H_{19}N_2O_4$ : C, 49.99; H, 7.46. Found: C, 50.58; H, 7.05.

**N-Nitroso-N-benzoyl-L-leucine Methyl Ester (IIIb).**—Nitrosation of 99 mg. of oily nitroso derivative from 95 mg. of N-benzoyl-L-leucine methyl ester<sup>21</sup>;  $\lambda_{\max} 5.72$  and  $5.88 \mu$ ; ultraviolet in isoctane:  $\epsilon_{390}^{\text{shoulder}} 41$ ,  $\epsilon_{405}^{\text{max}} 64$ ,  $\epsilon_{415}^{\text{min}} 53$ ,  $\epsilon_{425}^{\text{max}} 64$ ; R.D. in isoctane ( $c$  0.094 to 305 m $\mu$ , then 0.0036):  $[\alpha]_{700} -20^\circ$ ,  $[\alpha]_{589} -40^\circ$ ,  $[\alpha]_{470} -70^\circ$ ,  $[\alpha]_{425} +410^\circ$ ,  $[\alpha]_{415} -350^\circ$ ,  $[\alpha]_{408} -30^\circ$ ,  $[\alpha]_{398} -550^\circ$ ,  $[\alpha]_{391} -380^\circ$ ,  $[\alpha]_{380} -580^\circ$ ,  $[\alpha]_{362.5} -620^\circ$ ,  $[\alpha]_{357.5} -600^\circ$ ,  $[\alpha]_{304} -1300^\circ$ ,  $[\alpha]_{271} +440^\circ$ .

*Anal.* Calcd. for  $C_{14}H_{18}N_2O_4$ : C, 60.42; H, 6.52. Found: C, 60.69; H, 6.70.

**N-Nitroso-N-benzoyl-L-glutamic Acid Diethyl Ester (IIIc).**—Nitrosation of 133 mg. of N-benzoyl diethyl L-glutamate<sup>22</sup> led to 140 mg. of oily N-nitroso derivative,  $\lambda_{\max} 5.80$  and  $5.90 \mu$ ; ultraviolet in isoctane:  $\epsilon_{390}^{\text{shoulder}} 49$ ,  $\epsilon_{405}^{\text{max}} 79$ ,  $\epsilon_{415}^{\text{min}} 60$ ,  $\epsilon_{425}^{\text{max}} 80$ ; R.D. (Fig. 3) in isoctane ( $c$  0.405):  $[\alpha]_{700} -207^\circ$ ,  $[\alpha]_{589} -229^\circ$ ,  $[\alpha]_{433} -544^\circ$ ,  $[\alpha]_{424} -266^\circ$ ,  $[\alpha]_{415} -370^\circ$ ,  $[\alpha]_{406} -232^\circ$ ,  $[\alpha]_{399} -308^\circ$ ,  $[\alpha]_{390} -237^\circ$ ,  $[\alpha]_{382.5} -323^\circ$ ,  $[\alpha]_{377.5} -315^\circ$ ,  $[\alpha]_{303} -868^\circ$ .

*Anal.* Calcd. for  $C_{16}H_{20}N_2O_6$ : C, 57.13; H, 5.98; N, 8.33. Found: C, 56.50; H, 5.75; N, 7.88.

**N-Nitroso-N-benzoyl-O-acetyl-L-serine Methyl Ester (III d).**—N-Benzoyl-L-serine methyl ester<sup>23</sup> was acetylated by heating with acetic anhydride-pyridine for 2 hr. and the resulting N-benzoyl-O-acetyl derivative was recrystallized from dilute ethanol: m.p. 89–90°,  $[\alpha]_D -62.7^\circ$  ( $c$  3.82 in chloroform),  $\lambda_{\max}^{\text{nujol}} 3.02, 5.73, 5.78$  and  $6.10 \mu$ .

*Anal.* Calcd. for  $C_{13}H_{15}NO_5$ : C, 58.86; H, 5.70; N, 5.28. Found: C, 59.04; H, 5.68; N, 6.38.

Nitrosation of 76 mg. of the above N-benzoyl-O-acetate provided 81 mg. of the oily nitroso derivative,  $\lambda_{\max} 5.78$  and  $5.90 \mu$ ; ultraviolet in dioxane:  $\epsilon_{390}^{\text{shoulder}} 52$ ,  $\epsilon_{405}^{\text{max}} 80$ ,  $\epsilon_{415}^{\text{min}} 63$ ,  $\epsilon_{425}^{\text{max}} 78$ ; R.D. (Fig. 3) in dioxane ( $c$  0.535):  $[\alpha]_{700} -28^\circ$ ,  $[\alpha]_{589} -49^\circ$ ,  $[\alpha]_{460} -84^\circ$ ,  $[\alpha]_{425} +35^\circ$ ,  $[\alpha]_{412} -163^\circ$ ,  $[\alpha]_{405} -126^\circ$ ,  $[\alpha]_{397.5} -245^\circ$ ,  $[\alpha]_{390} -227^\circ$ ,  $[\alpha]_{380} -271^\circ$ ,  $[\alpha]_{370} -251^\circ$ ,  $[\alpha]_{325} -294^\circ$ .

*Anal.* Calcd. for  $C_{13}H_{14}N_2O_6$ : C, 53.06; H, 4.80; N, 9.52. Found: C, 53.10; H, 4.71; N, 9.48.

**N-Nitroso-N-benzoyl-L-aspartic Acid Diethyl Ester (III e).**—Nitrosation of diethyl N-benzoyl-L-aspartate<sup>24</sup> afforded a low melting solid (m.p. below 25°);  $\lambda_{\max} 5.78$  and  $5.90 \mu$ ; ultraviolet in isoctane:  $\epsilon_{390}^{\text{shoulder}} 59$ ,  $\epsilon_{405}^{\text{max}} 85$ ,  $\epsilon_{415}^{\text{min}} 62$ ,  $\epsilon_{425}^{\text{max}} 82$ ; R.D. in isoctane ( $c$  0.39 to 310 m $\mu$ , then 0.078):  $[\alpha]_{700} -92^\circ$ ,  $[\alpha]_{589} -133^\circ$ ,  $[\alpha]_{433} -230^\circ$ ,  $[\alpha]_{427.5} -212^\circ$ ,  $[\alpha]_{421} -333^\circ$ ,  $[\alpha]_{410} -235^\circ$ ,  $[\alpha]_{400} -373^\circ$ ,  $[\alpha]_{392.5} -320^\circ$ ,  $[\alpha]_{380} -392^\circ$ ,  $[\alpha]_{375} -385^\circ$ ,  $[\alpha]_{300} -1010^\circ$ ,  $[\alpha]_{280} -537^\circ$ .

*Anal.* Calcd. for  $C_{15}H_{19}N_2O_6$ : C, 55.89; H, 5.63; N, 8.69. Found: C, 55.84; H, 5.89; N, 8.48.

**N-Nitroso-N-benzoyl-L-alanine Methyl Ester (III f).**—The nitroso derivative III f was obtained in quantitative yield as an oil from N-benzoyl-L-alanine methyl ester<sup>25</sup>;  $\lambda_{\max} 5.75$  and  $5.90 \mu$ ; ultraviolet in isoctane:  $\epsilon_{390}^{\text{shoulder}} 59$ ,  $\epsilon_{407}^{\text{max}} 96$ ,  $\epsilon_{415}^{\text{min}} 71$ ,  $\epsilon_{425}^{\text{max}} 95$ ; R.D. in isoctane ( $c$  0.5

320 m $\mu$ , then 0.10):  $[\alpha]_{700} -86^\circ$ ,  $[\alpha]_{589} -112^\circ$ ,  $[\alpha]_{490} -152^\circ$  (infl.),  $[\alpha]_{450} -230^\circ$  (infl.),  $[\alpha]_{430} -276^\circ$ ,  $[\alpha]_{407.5} -160^\circ$ ,  $[\alpha]_{400} -166^\circ$ ,  $[\alpha]_{392.5} -122^\circ$ ,  $[\alpha]_{382.5} -164^\circ$ ,  $[\alpha]_{310} -570^\circ$ ,  $[\alpha]_{300} -460^\circ$ .

*Anal.* Calcd. for  $C_{11}H_{12}N_2O_4$ : C, 55.93; H, 5.14; N, 11.86. Found: C, 55.93; H, 5.15; N, 11.67.

**N-Nitroso-N-acetyl-L-alanine methyl ester (III g)<sup>26</sup>.** R.D. in isoctane ( $c$  0.585 to 412.5 m $\mu$ , then 0.117):  $[\alpha]_{700} -26^\circ$ ,  $[\alpha]_{589} -41^\circ$ ,  $[\alpha]_{430} -100^\circ$  (infl.),  $[\alpha]_{432.5} -82^\circ$ ,  $[\alpha]_{422.5} -87^\circ$ ,  $[\alpha]_{407.5} +2^\circ$ ,  $[\alpha]_{400} -97^\circ$ ,  $[\alpha]_{390} +20^\circ$ ,  $[\alpha]_{382.5} -73^\circ$ ,  $[\alpha]_{377.5} +1^\circ$ ,  $[\alpha]_{362.5} -52^\circ$  (infl.),  $[\alpha]_{347.5} -96^\circ$  (infl.),  $[\alpha]_{312.5} -200^\circ$ .

**N-Nitroso-N-benzoyl-L-phenylalanine Methyl Ester (III h).**—Nitrosation of 60 mg. of N-benzoyl-L-phenylalanine methyl ester<sup>27</sup> afforded 66 mg. of the oily nitroso derivative III h,  $\lambda_{\max} 5.73$  and  $5.86 \mu$ ; ultraviolet in isoctane:  $\epsilon_{390}^{\text{shoulder}} 49$ ,  $\epsilon_{405}^{\text{max}} 73$ ,  $\epsilon_{415}^{\text{min}} 57$ ,  $\epsilon_{425}^{\text{max}} 75$ ; R.D. in isoctane ( $c$  0.206 to 375 m $\mu$ , then 0.041):  $[\alpha]_{550} -84^\circ$ ,  $[\alpha]_{589} -119^\circ$ ,  $[\alpha]_{475} -189^\circ$  (plateau),  $[\alpha]_{428} +52^\circ$ ,  $[\alpha]_{412} -453^\circ$ ,  $[\alpha]_{405} -392^\circ$ ,  $[\alpha]_{390} -733^\circ$  (infl.),  $[\alpha]_{370} -847^\circ$  (infl.),  $[\alpha]_{310} -1690^\circ$ ,  $[\alpha]_{285} -1110^\circ$ .

*Anal.* Calcd. for  $C_{17}H_{16}N_2O_4$ : C, 65.37; H, 5.16. Found: C, 65.30; H, 5.30.

**N-Nitroso-N-acetyl-(+)-1,2,2-triphenylethylamine (IV)<sup>15</sup>.** Ultraviolet absorption in absolute ethanol:  $\epsilon_{390}^{\text{shoulder}} 76$ ,  $\epsilon_{407}^{\text{max}} 110$ ,  $\epsilon_{415}^{\text{min}} 87$ ,  $\epsilon_{427}^{\text{max}} 111$ ; R.D. (Fig. 3) in isoctane ( $c$  0.104):  $[\alpha]_{700} +115^\circ$ ,  $[\alpha]_{589} +180^\circ$ ,  $[\alpha]_{470} +310^\circ$  (infl.),  $[\alpha]_{465} +350^\circ$  (infl.),  $[\alpha]_{450} +480^\circ$ ,  $[\alpha]_{435} +230^\circ$ ,  $[\alpha]_{430} +420^\circ$ ,  $[\alpha]_{427} +210^\circ$ ,  $[\alpha]_{422} +440^\circ$ ,  $[\alpha]_{415} +270^\circ$ ,  $[\alpha]_{412} +350^\circ$ ,  $[\alpha]_{407} +200^\circ$ ,  $[\alpha]_{400} +380^\circ$ ,  $[\alpha]_{396} +340^\circ$ ,  $[\alpha]_{394} +360^\circ$ ,  $[\alpha]_{390} +330^\circ$ ,  $[\alpha]_{390} +226^\circ$ .

**N-Nitroso-N-methyl-(+)- $\alpha$ -methylbutyramide (V).**—(+)- $\alpha$ -Methylbutyric acid was transformed into its N-methylamide (m.p. 38–40°,  $[\alpha]_D +23^\circ$  ( $c$  6.6 in chloroform),  $\lambda_{\max} 3.10$  and  $6.15 \mu$ ) and then nitrosated in quantitative yield to the yellow oil V,  $\lambda_{\max} 5.78 \mu$ ; ultraviolet in isoctane:  $\epsilon_{377}^{\text{shoulder}} 71$ ,  $\epsilon_{392}^{\text{max}} 75$ ,  $\epsilon_{392}^{\text{min}} 53$ ,  $\epsilon_{405}^{\text{max}} 138$ ,  $\epsilon_{415}^{\text{min}} 51$ ,  $\epsilon_{426}^{\text{max}} 174$ ; R.D. (Fig. 4) in isoctane ( $c$  0.45):  $[\alpha]_{700} +14^\circ$ ,  $[\alpha]_{589} +9^\circ$ ,  $[\alpha]_{437} -73^\circ$ ,  $[\alpha]_{425} +46^\circ$ ,  $[\alpha]_{421.5} -64^\circ$ ,  $[\alpha]_{408} +186^\circ$ ,  $[\alpha]_{402.5} +127^\circ$ ,  $[\alpha]_{392.5} +246^\circ$ ,  $[\alpha]_{386} +137^\circ$ ,  $[\alpha]_{377.5} +215^\circ$ ,  $[\alpha]_{372.5} +190^\circ$ ,  $[\alpha]_{362.5} +199^\circ$ ,  $[\alpha]_{305} +133^\circ$ .

*Anal.* Calcd. for  $C_8H_{12}N_2O_2$ : C, 49.98; H, 8.39; N, 19.43. Found: C, 50.22; H, 8.30; N, 19.39.

**N-Nitroso-N-methyl-(+)- $\alpha$ -(2-naphthoxy)-propionamide (VI).**—(+)- $\alpha$ -(2-Naphthoxy)-propionic acid<sup>17</sup> in ether solution was converted into its acid chloride with thionyl chloride in the presence of pyridine. After stirring at 0° for 30 min., excess methylamine in benzene was added and the mixture agitated at room temperature for 1 hr. Filtration, evaporation to dryness and recrystallization from cyclohexane afforded colorless crystals of the N-methylamide, m.p. 136–137°.

*Anal.* Calcd. for  $C_{14}H_{15}NO_2$ : C, 73.34; H, 6.59; N, 6.11. Found: C, 73.21; H, 6.70; N, 6.11.

Nitrosation of 71 mg. of this amide gave 77 mg. of yellow crystals of VI, m.p. 81–82°,  $\lambda_{\max}^{\text{nujol}} 5.80 \mu$ ; ultraviolet in dioxane:  $\epsilon_{375}^{\text{shoulder}} 180$ ,  $\epsilon_{380}^{\text{min}} 170$ ,  $\epsilon_{390}^{\text{max}} 190$ ,  $\epsilon_{395}^{\text{min}} 170$ ,  $\epsilon_{408}^{\text{max}} 230$ ,  $\epsilon_{418}^{\text{min}} 150$ ,  $\epsilon_{425}^{\text{max}} 230$ ; R.D. (Fig. 4) in dioxane ( $c$  0.093 to 340 m $\mu$ , then 0.0036):  $[\alpha]_{700} +30^\circ$ ,  $[\alpha]_{589} +110^\circ$ ,  $[\alpha]_{496} +280^\circ$ ,  $[\alpha]_{475} +250^\circ$ ,  $[\alpha]_{450} +400^\circ$  (infl.),  $[\alpha]_{427.5} +800^\circ$ ,  $[\alpha]_{404} +280^\circ$ ,  $[\alpha]_{390} -220^\circ$ ,  $[\alpha]_{375} -160^\circ$ ,  $[\alpha]_{366} -210^\circ$ ,  $[\alpha]_{350} -90^\circ$ ,  $[\alpha]_{323} -330^\circ$ ,  $[\alpha]_{288} +780^\circ$ .

*Anal.* Calcd. for  $C_{14}H_{14}N_2O_3$ : C, 65.10; H, 5.46; N, 10.85. Found: C, 65.08; H, 5.20; N, 11.01.

**N-Nitroso-N-methyl-(+)- $\alpha$ -phenylbutyramide (VII).**—The yellow solid (116 mg.) obtained on nitrosation of 100 mg. of the N-methylamide<sup>28</sup> of (+)- $\alpha$ -phenylbutyric acid melted at room temperature;  $\lambda_{\max} 5.80 \mu$ ; ultraviolet in

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*Anal.* Calcd. for  $C_{11}H_{15}NO$ : C, 74.54; H, 8.53; N, 7.91. Found: C, 74.51; H, 8.58; N, 7.85.

dioxane:  $\epsilon_{382}^{\text{shoulder}}$  94,  $\epsilon_{395}^{\text{min}}$  84,  $\epsilon_{405}^{\text{max}}$  95,  $\epsilon_{415}^{\text{min}}$  63,  $\epsilon_{425}^{\text{max}}$  80; R.D. (Fig. 4) in dioxane (*c* 0.078):  $[\alpha]_{700} +15^\circ$ ,  $[\alpha]_{589} +70^\circ$ ,  $[\alpha]_{428} -900^\circ$ ,  $[\alpha]_{418-407} +250^\circ$  (plateau),  $[\alpha]_{392-390} +530^\circ$  (plateau),  $[\alpha]_{355} +370^\circ$ ,  $[\alpha]_{350} +400^\circ$ ,  $[\alpha]_{335} +350^\circ$ ,  $[\alpha]_{315} +360^\circ$ .

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$ : C, 64.06; H, 6.84; N, 13.58. Found: C, 63.82; H, 6.31; N, 13.49.

**N-Nitroso-N-methyl-O-acetyl-D-lactamide (VIII).**—Commercially available (California Corporation for Biochemical Research, Los Angeles) calcium D-lactate tetrahydrate was transformed into the anhydrous acid, thence the acid chloride (with phosphorus trichloride) and then the N-methylamide, which exhibited m.p. 68–69° after re-

crystallization from ether-petroleum ether;  $[\alpha]_{\text{D}} +6.9^\circ$  (*c* 5.5 in chloroform),  $\lambda_{\text{max}}^{\text{N}^{\text{vis}}}$  3.02, 5.78 and 6.06  $\mu$ .

*Anal.* Calcd. for  $\text{C}_8\text{H}_{11}\text{NO}_3$ : C, 49.64; H, 7.64; N, 9.65. Found: C, 49.86; H, 7.64; N, 9.69.

The nitroso derivative VIII was obtained in nearly quantitative yield as a yellow oil,  $\lambda_{\text{max}}$  5.7–5.8  $\mu$ ; ultra-violet in dioxane:  $\epsilon_{390}^{\text{shoulder}}$  67,  $\epsilon_{404}^{\text{max}}$  111,  $\epsilon_{418}^{\text{min}}$  69,  $\epsilon_{430}^{\text{max}}$  97; R.D. (Fig. 4) in dioxane (*c* 0.615):  $[\alpha]_{700} +14^\circ$ ,  $[\alpha]_{589} +13^\circ$ ,  $[\alpha]_{440} -120^\circ$ ,  $[\alpha]_{435} -149^\circ$ ,  $[\alpha]_{422.5} -150^\circ$ ,  $[\alpha]_{417.5} -276^\circ$ ,  $[\alpha]_{405} -101^\circ$ ,  $[\alpha]_{375} +263^\circ$ ,  $[\alpha]_{310} +42^\circ$ .

*Anal.* Calcd. for  $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_4$ : C, 41.38; H, 5.79; N, 16.09. Found: C, 41.91; H, 5.99; N, 15.80.

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## The Association of $\alpha$ - and $\beta$ -Cyclodextrins with Organic Acids<sup>1</sup>

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Solubilities of organic acids have been determined in order to study their association with  $\alpha$ - and  $\beta$ -cyclodextrins in water. The cyclodextrins increase the solubilities of acids which easily form crystalline inclusion complexes with them (caproic to lauric acid). Acids from which such complexes have not been obtained, or have been obtained only under extreme conditions, still may exhibit increased solubility (benzoic and iodobenzoic acids). Acids having still larger diameter are much less, if at all, affected (durylcarboxylic to 4-durylbutyric acids), and show extremely high component ratios cyclodextrin/acid in solution. The association of the acids which brings about the higher solubility obviously follows an inclusion mechanism. The compatibility of the whole acid molecule with the void inside the cyclodextrins is a deciding factor. Fatty acids follow the principle of preferential placing in crystalline dehydrated complexes of cyclodextrins. They are mostly "crowded," while "loose" packing is encountered with benzoic and *p*-iodobenzoic acids.  $\text{I}^-$  outranks other ions in preventing the association of organic acids with  $\alpha$ -cyclodextrin. This is in accord with the great affinity of  $\text{I}^-$  to amylose-type carbohydrates, which has been demonstrated by other investigators. The optical rotations of cyclodextrins are changed when they are associated with other molecules. The changes appear to be related to the structure of the latter.

### Introduction

The terms "inclusion compound" or "clathrate" have been coined to describe the positional relationship of two components which form certain types of crystals. Often the components are designated as host and guest, again in reference to the solid state. Some evidence for association of host with guest molecules in the liquid phase has been advanced for urea and straight-chain aliphatic compounds<sup>2,3</sup> which are potential guest molecules in the crystalline phase. Complete dissociation in solution, however, has been claimed for the complexes of deoxycholic acid.<sup>4</sup> More recently, association phenomena in aqueous solutions have been studied utilizing  $\alpha$ -,  $\beta$ - and  $\gamma$ -cyclodextrins ( $\alpha$ -,  $\beta$ -,  $\gamma$ -CDX), or in more significant nomenclature, cyclohexa-, hepta- and -octaamylose.<sup>5</sup> While usually several host molecules are needed to provide the encasing structure, one molecule of cyclodextrin offers the geometry necessary for inclusion. With it, inclusion is not necessarily restricted to the crystalline phase, but may also take place in solution. Under this assumption, Cramer, Lautsch and co-workers investigated reactions inducing optical asymmetry, rates of dehydrogenation,

enzymatic processes, spectra of dyestuffs and oxidation-reduction potentials in solutions of cyclodextrins.<sup>6</sup> The greater part of these and similar investigations<sup>7-9</sup> was carried out with reference to the mode of enzyme action. Much less effort was made to detail the steric conditions which might influence the association of cyclodextrins with other molecules in solution. Steric considerations are a major objective of this report which is restricted to the association of cyclodextrins with molecules of rather simple structure.

It has been found that the solubility of benzoic acid is increased by the presence of  $\alpha$ - and  $\beta$ -cyclodextrins. The presence of ions greatly influences the solubilities and, implicitly, the association.<sup>10</sup> Therefore, it was desirable to avoid methods that involve buffer or other extraneous components in the associating systems. Experiments with aminobenzoic acids and some other acids having amino groups showed it advisable to correlate only results obtained from one type of compound. Organic acids without additional functional groups were chosen here and their solubilities were taken as a criterion for association with  $\alpha$ - and  $\beta$ -cyclodextrins in water.

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