

*Anal.* Calcd for  $C_{13}H_{19}NO_5$ : C, 54.75; H, 6.72; N, 4.91. Found: C, 54.50; H, 6.65; N, 5.19.

**DL- $\alpha$ -Acetamido- $\alpha$ -vanillylpropionic Acid (X).**—Hydrolysis of VII using the identical procedure as used for L-VII gave 20.0 g (93% yield), mp 213–216°. Crystallization from water provided the analytical sample, mp 218–220°.

*Anal.* Calcd for  $C_{13}H_{17}NO_5$ : C, 58.42; H, 6.41; N, 5.24. Found: C, 58.56; H, 6.21; N, 5.38.

**L- $\alpha$ -Methyl-3-methoxy-4-hydroxyphenylalanine (L-XI).**—L-VII (100 g) was added portionwise to cold concentrated hydrochloric acid (200 ml). The solution was diluted with water (1 l.) and the mixture refluxed for 5 hr. After cooling to 20°, the pH was adjusted to 5.0 with concentrated ammonium hydroxide. The product was filtered, washed free of chlorides with water, and vacuum dried to yield 87.7 g, mp 307° dec. The analytical sample was prepared by dissolving crude L-XI in dilute hydrochloric acid, treating with Darco G-60, and reprecipitating as the monohydrate by adjusting to pH 5.5: mp 313° dec;  $[\alpha]_{D_{25}}^{25} +166^\circ$  (c 0.5, copper sulfate solution);<sup>2</sup> H<sub>2</sub>O, 8.0% (Karl Fischer) (calcd 7.5%). A single spot appeared on paper strip chromatography using a *n*-BuOH-H<sub>2</sub>O-HOAc system (120:50:30). The sample (spotted as 1% solution in water saturated with sulfur dioxide) was detected by

spraying with diazotized *p*-nitroaniline, drying, and spraying with 5% sodium carbonate solution.

*Anal.* Calcd for  $C_{11}H_{15}NO_4$ : C, 58.65; H, 6.71. Found: C, 58.66; H, 6.42. (Sample dried at 100°.)

**DL- $\alpha$ -Methyl-3-methoxy-4-hydroxyphenylalanine (XI).**—The DL-N-acetylaminonitrile VII (20.0 g) was dissolved in concentrated hydrochloric acid (40 ml), diluted with water (40 ml), and heated at 90° for 4 hr until solution was complete. The water was removed at reduced pressure and the residue dissolved in water. Adjustment to pH 6.0 with concentrated ammonium hydroxide resulted in the precipitation of the amino acid. The product was filtered, washed with water, and vacuum dried to give 17.75 g (97.5% yield), mp 318–320° dec.

*Anal.* Calcd for  $C_{11}H_{15}NO_4$ : C, 58.65; H, 6.71. Found: C, 58.40; H, 6.60.

**Registry No.**—II, 6555-27-7; L-II, 14818-96-3; III, 15073-71-9; V, 15073-82-2; VI, 555-30-6; VII, 14818-97-4; L-VII, 14818-98-5; VIII, 15073-74-2; L-VIII, 15073-76-4; IX, 15156-57-7; L-IX, 15073-77-5; X, 15073-78-6; L-X, 15073-79-7; XI, 15073-80-8; L-XI, 6739-31-7.

## The Racemization of $\alpha$ -Methyl- $\alpha$ -acetamidonitriles

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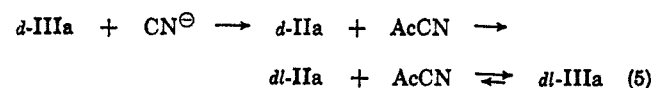
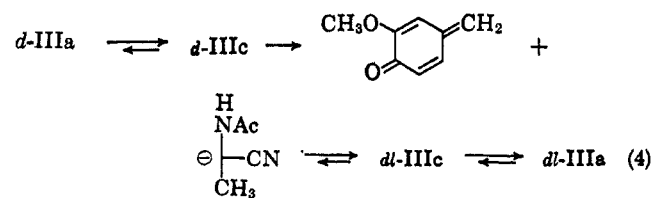
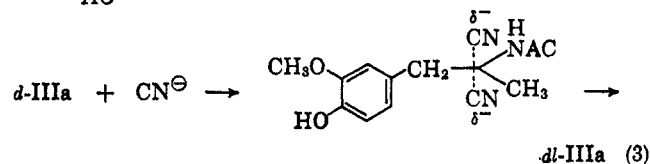
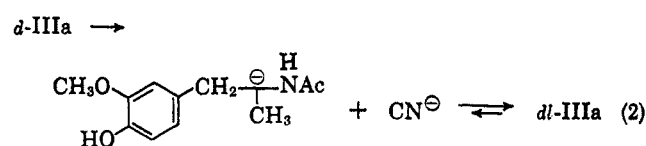
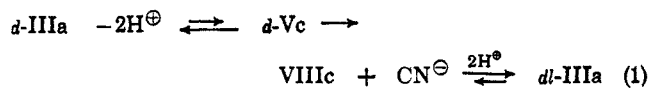
The mechanism of base-catalyzed racemization of  $\alpha$ -acetamidonitriles bearing no enolizable  $\alpha$  hydrogen has been studied and found to proceed *via* elimination and readdition of the elements of HCN; the amide nitrogen must bear a hydrogen atom. The rate-determining step is not deprotonation but expulsion of cyanide from the amide anion.

In the production of L- $\alpha$ -methyl-dopa *via* the amino-nitrile route, resolution can be accomplished on either the amino acid itself,<sup>1</sup> the  $\alpha$ -amino-2-vanillylpropionitrile IIa,<sup>2</sup> or the  $\alpha$ -acetamido- $\alpha$ -vanillylpropionitrile IIIa.<sup>2</sup> Both enantiomers can be utilized if the unwanted *D* isomer can be racemized. This cannot be done at present with I, and, although racemization of II is facile, its resolution is not. Compound IIIa, however, crystallizes as a *dl* mixture, and its resolution by spontaneous crystallization has been accomplished; thus racemization of *D*-IIIa became a paramount goal.

This was eventually achieved using sodium cyanide in DMSO. A preliminary description of this method is contained in the accompanying paper,<sup>2</sup> and we here report details of the reaction and its mechanism. The first portion of the study was concerned with the scope of the reaction, and the second with kinetics.

Although it was found that IIIa could be racemized by any base of sufficient strength and solubility, sodium cyanide was used in most of the work because it gave the best yields, presumably by suppressing loss of cyanide from the product. In dry DMSO, IIIa could be conveniently racemized in high yield at temperatures ranging from about 140° to reflux (189°). The rate increased about threefold for each 10° rise in temperature. A selection of racemization data obtained in DMSO is presented in Table I.

Five mechanisms were originally considered for the reaction (eq 1–5).



(1) E. W. Tristram, J. ten Broeke, D. F. Reinhold, M. Sletzing, and D. E. Williams, *J. Org. Chem.*, **29**, 2053 (1964).

(2) D. F. Reinhold, R. A. Firestone, W. A. Gaines, J. M. Chemerda, and M. Sletzing, *J. Org. Chem.*, **33**, 1209 (1968).

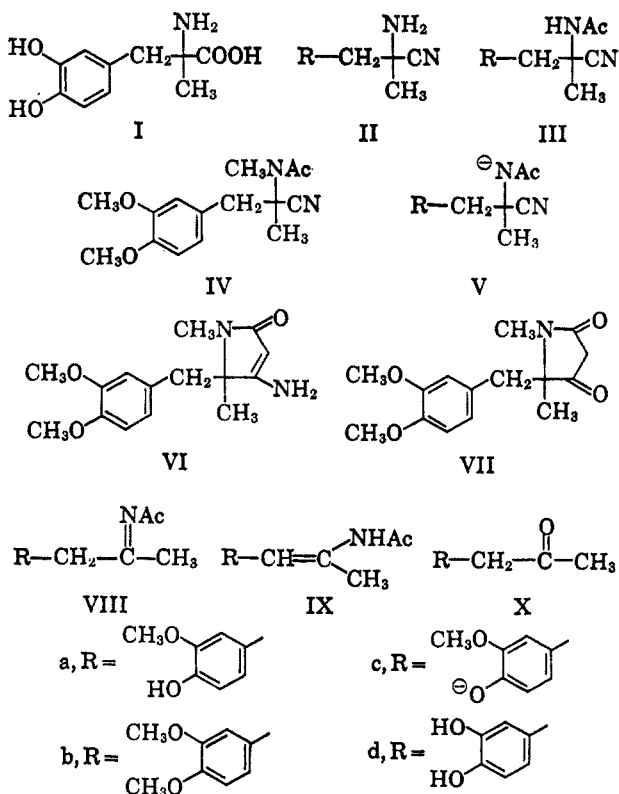
Direct ionization (eq 2) was eliminated by the observation that racemization did not occur in the

TABLE I<sup>a</sup>  
 RACEMIZATION OF VARIOUS  $\alpha$ -METHYL- $\alpha$ -ACETAMIDONITRILES

Run no.	Compd	Base (moles)	Temp, °C	Time, min	% racemization	% yield
1 <sup>b</sup>	IIIa	NaCN (2)	160	10	54	83
2	IIIa	NaCN (2)	160	10	83	86
3	IIIa	NaCN (0.5)	160	10	64	94
4	IIIa	NaH (0.5)	160	10	94	82
5	IIIa	Na <sub>2</sub> CO <sub>3</sub> (0.5)	160	10	18	80
6	IIIa	CaO (excess)	160	10	0	94
7	IIIa	Hg(CN) <sub>2</sub> (0.5)	189	3	0	50
8	IIIa	NaCN (0.5), NaH (1)	140	10	67	89
9	IIIa	NaCN (0.5), HCN (1)	160	10	36	83
10	IIIa	NaCN (0.5)	150	10	18	90
11	IIIa	KCN (0.5)	150	10	17	89
12	IIIb	NaCN (0.5)	160	10	100	92
13	IIIb	NaH (0.5)	160	10	100	75
14	IIIb	None	160	10	0	95
15	IV	NaCN (0.5)	160	10	0	75 <sup>c</sup>
16	IIIa	NaH (2)	25	120	12	94
17	IIIc	NaCN (0.5)	160	30	38	>90
18	IIIa	NaCN (0.5)	189	1.5	100	91
19 <sup>d</sup>	IIIa	NaCN (0.5)	210	5	45	50
20 <sup>b</sup>	IIIa	NaCN (0.5)	189	1.5	100	96

<sup>a</sup> 20% in DMSO. <sup>b</sup> 33% in DMSO. <sup>c</sup> 91% yield taking cyclization into account. <sup>d</sup> No solvent.

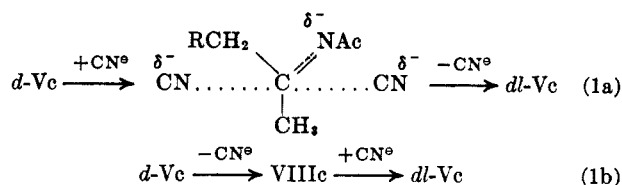
absence of base (compare runs 14 with 12 and 13). The case in eq 4, which requires that the dimethoxy derivative IIIb be optically stable under our conditions, was disproved by the finding that IIIb actually racemized much faster than IIIa (compare runs 12 and 3).



If eq 1 is correct, replacement of the N-H by N-methyl must completely suppress the reaction. This is not the case with eq 3 and 5, although they might suffer some steric retardation. When IV was subjected to the usual racemization conditions (run 15), no loss of optical activity was observed; thus the amide N-H is essential for racemization.

These experiments left the mechanism in eq 1 as the only important possibility left from the group. How-

ever, the question still remained whether the incoming cyanide approaches the molecule before (eq 1a) or after (eq 1b) complete separation of the outgoing cyanide. A clear choice can be made by comparing



the rate of racemization with that of exchange with external radioactive cyanide. In the mechanism of eq 1a, each exchange of cyanide requires an inversion and racemizes two molecules, while with that of eq 1b only one molecule racemizes per exchange.

The kinetic expressions<sup>3</sup> for the two cases given in eq 1a and b are, respectively

$$\frac{1 - F_{ex}}{1 - F_{ex}^2} = (1 - F_r)^{3/2}$$

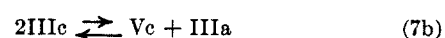
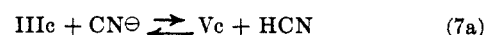
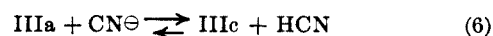
In these expressions,  $F_r$  = fraction racemized and  $F_{ex}$  = radioactivity at time  $t$  divided by radioactivity at time  $\infty$ . A sample of pure IIIa reacted in the presence of C<sup>14</sup>-labeled cyanide ion and was recovered in 90.4% yield with 17.8% racemization. The calculated  $F_{ex}$  for cases in eq 1a and b are 0.256 and 0.444, respectively, and the  $F_{ex}$  observed was 0.460. This result unequivocally supports mechanism of eq 1b, the elimination-addition route.

The chronology of this elimination remains to be established. It seemed intuitively obvious that the removal of the proton on the amide nitrogen atom would be rate controlling, because elimination of cyanide ion from the resulting anion would surely be rapid compared with the neutral molecule IIa, which loses cyanide ion so readily.<sup>2</sup> This analogy, in the event, proved misleading.

It was found that compound IIIa could be treated with 2 moles of sodium hydride for 2 hr at 25° in DMSO and recovered in 94% yield in 88% of its original optical activity (run 16). To show that all of the hydride was reacting, the hydrogen evolved was collected in 96% yield. Finally, the possibility that 1 mole of the hydrogen came from reaction with DMSO rather than with the amide N-H was eliminated by dimethylation. Compound IV could be prepared from IIIa in >72% yield by treating IIIa with 2 moles of sodium hydride in DMSO followed by dimethyl sulfate.

We conclude, then, that IIIa can maintain its optical asymmetry even with anionic amide nitrogen and that deprotonation of this atom is not rate controlling. The most probable mechanism for the racemization of III has the elimination of cyanide ion from the amide anion as the rate-determining step.

A more complete picture of the reaction can now be written (eq 6-8).



(3) These expressions were derived for us by Dr. R. T. Mullen.

**Kinetic Studies.**—Rate constants were determined for the racemization of IIIa, IIIb (see Table II), IIIc, and Vb.

TABLE II

KINETICS OF RACEMIZATION OF IIIa AND IIIb

Run no.	Temp, °C	Substrate	Concn, M	NaCN, M	$k_1$ , hr <sup>-1</sup>	$k_2$ , l. mole <sup>-1</sup> hr <sup>-1</sup>
K1	124.8	IIIa	0.815	0.0787	0.034	0.47
K2	138.6	IIIa	0.815	0.0787	0.18	2.5
K3	131.2	IIIa	0.815	0.0787	0.076	1.06
K4	138.8	IIIa	0.814	0.0409	0.097	2.6
K5	139.2	IIIa	0.402	0.0392	0.27	7.7
K6	117.4	IIIb	0.802	0.0787	0.17	2.3
K7	117.5	IIIa	0.798	0.847 <sup>a</sup>	0.95	1.21
K8	110.2	IIIa	0.798	0.847 <sup>a</sup>	0.44	0.56

<sup>a</sup> Flushed twice *in vacuo* with DMSO before racemization. This converts IIIa into IIIc (*vide infra*).

During the first portion of the work, reactions were run in sealed tubes, using DMSO and NaCN. Under these conditions, several acid-base equilibria must be brought into existence before the appearance of V, the amide anion, whose expulsion of cyanide ion is the slow step in the racemization.

The second portion of the kinetic study was concerned with this reaction. Conditions were chosen where all ionizable protons were removed so that all preequilibria were forced completely to the right. The base employed was sodium methylsulfinylmethylide (dimethylsodium) in 1% molar excess, which was prepared and standardized daily. Kinetic runs were performed in volumetric flasks, using a constant-temperature bath good to  $\pm 0.02^\circ$ . For reasons discussed below, these runs did not produce linear plots, but the initial curvature was slight enough to permit the determination of fairly accurate initial rate constants. In these experiments, Vb was used rather than Va, which oxidizes rapidly in very strong base. It may be noted that the return of cyanide to the molecule after elimination is far from quantitative under these conditions; this does not, however, diminish the significance of the results, since departure of the cyanide leads directly to symmetric products, whose subsequent fate is kinetically not significant.

All but one of the sodium cyanide runs were pseudo first order as far as they were carried (20–92% completion). The one exception, run K4, was first order to about 40% reaction, after which the rate began to diminish. We attribute this to the exceptionally low base concentration in this run, 5 mole %; even a very small loss of base by side reactions (*vide infra*) would be magnified in relation to the total.

That the reaction is actually first order in base concentration as well as in substrate can be seen by comparing runs K2 and K4. The second-order rate constants (corrected for the small temperature difference) are the same despite a twofold change in the amount of catalyst.

The very high rates of racemization of Vc (run 16) and of Vb (K13, K14, and K16) (see Table III) compared with those of IIIa and IIIb (runs 1–14), indicate that the steady-state concentration of intermediates V is very low under normal racemization conditions. Chiefly responsible for this is the unfavorable equilibrium in eq 7a and b because equilibrium 6 lies considerably to the right. This was deduced from the follow-

TABLE III

KINETICS OF RACEMIZATION OF Va

Run no.	Temp, °C	Concn, M	$k_1$ , hr <sup>-1</sup>
K13	30.06	0.793	0.18
K14	30.06	0.402	0.18
K16	37.06	0.855	0.42

ing facts: first, if the equilibrium constant for eq 6 were very small, the addition of molar quantities of HCN to the reaction would have a much larger effect on the rate than it actually does (compare runs 3 and 9), which is to reduce it about twofold; second it is possible to remove cyanide by distillation very easily from reaction mixtures containing IIIa and NaCN. This fact made it possible to run kinetics on the vanillyl phenoxide sodium salt IIIc (runs K7 and K8), which has been difficult to prepare by other methods.

TABLE IV

ACTIVATION CONSTANTS

Reaction	$E_a$ , kcal/mole	$A$ , sec <sup>-1</sup>	$S^\ddagger$ , eu
IIIa + NaCN	39	$1.5 \times 10^{16}$	13
IIIc + NaCN	30	$1.1 \times 10^{13}$	-1.4
Vb racemization	23	$2.2 \times 10^{12}$	-4.1

As expected, successively by-passing the preequilibria (eq 6 and 7) results in stepwise diminution of the activation energy (see Table IV).

**Effect of Hydrogen Bonding.**—The reactivity of anions is very great in polar aprotic solvents relative to protic ones,<sup>4</sup> and their basicity is markedly diminished by the introduction of even small amounts of proton donors.<sup>5</sup> This was borne out strongly in our work.

Large rate accelerations are brought about by the successive removal of active hydrogens from the vanillyl system. The most active hydrogen is the phenolic one, and methylation of the free phenol in IIIa, converting it into IIIb, results in a rate increase of 12 (run K6 compared with K1–3 extrapolated to 117.4°; compare also runs 3 and 12). Removal of this same active hydrogen by sodium salt formation, giving IIIc, also accelerates the reaction, in this case by a factor of 6.4 (run K7; see also runs 3 and 4). It is interesting that IIIc is not so active as IIIb (matching second-order rate constants  $k_2$ ), showing that the expected superiority in reactivity of the dianion Va over that of the monoanion Vb is more than offset by the extra energy required to remove a second proton from anion IIIc. Conversely, the addition of an active hydrogen donor, HCN, reduces the rate of racemization; runs 3 and 9 show a rate factor of about 2. For the same reason, the dihydroxy derivative IIIId is about one-sixth as reactive as IIIa (runs 3 and 17).

Upon withdrawal of the last active hydrogen the greatest acceleration is produced; Vb racemizes more than 5000 times as fast as IIIb, comparing runs K13 and K16, extrapolated to 117.4°, with run K6. It is recognized that this large rate increase is not due solely to the active hydrogen effect, but it must nevertheless be a large factor.

(4) A. J. Parker, *Quart. Rev. (London)*, **16**, 163 (1962).

(5) E. C. Steiner and J. M. Gilbert, *J. Amer. Chem. Soc.*, **85**, 3054 (1963).

Another system with no active hydrogen is IV-DMSO, in which the normally unreactive  $\alpha$  hydrogen of the acetamide function became readily removable with base. Cyclization to VI was quite facile with sodium cyanide, and rapid with sodium hydride. Compound VI was characterized from physical data and also by hydrolysis to VII.

**Effect of Solvent.**—Although DMSO appears to be the best solvent for the reaction, other polar aprotic solvents have been used successfully. In DMF at 153° the rate is about the same as in DMSO. Diglyme was a much poorer racemization medium, affording only 15% reaction after 10 min at 162° (cf. run 3).

With no added solvent, *i.e.*, with IIIa itself as reaction medium at 210°, racemization occurs, but slowly; compare runs 18 and 19. It was observed as a general phenomenon in the concentration range studied that the over-all velocity increased with dilution (run 1 *vs.* run 2) despite a second-order kinetic effect in the opposite direction. Runs K2 and K5 provide a quantitative comparison; at constant substrate-catalyst ratio, an increase of the per cent of DMSO from 80 to 90 gave rise to a second-order rate factor, corrected for temperature, of 2.7. This effect presumably stems not only from the lower polarity of IIIa but also from its possession of hydrogen bond donors.

It can be concluded, then, that an important function of DMSO in promoting our reaction is to tie up hydrogen bonds, thereby liberating a greater proportion of unencumbered base;<sup>6</sup> this, in turn, produces an augmented concentration of Vc by pushing equilibria (eq 7) to the right. Once the dianion Vc has been formed, however, polarity might have a *retarding* effect on its rate of dissociation, a transformation which dissipates charge. In the case of Vb, a monoanion, the solvent effect is small (cf. K13 and K14).

As expected, no racemization whatever was observed in diisobutyl carbinol after 30 min at 160°. This alcohol is sufficiently hindered that the carbonyl attack normally observed with bases in alcohols<sup>2</sup> could be at least partially suppressed, although only 45% recovery was obtainable.

**Side Reactions.**—The curvature of the semilog plots of runs K4, K13, K14, and K16, described previously, correspond to a slow diminution of the base concentration. In the dimethylsodium runs this is much more marked, and we attributed it to elimination and/or tautomerization reactions promoted by the exceptionally basic species present (*e.g.*, Vb,  $\text{CH}_3\text{SOCH}_2^\ominus$ , and  $\text{CN}^\ominus$  unencumbered by hydrogen bonds), in which relatively acidic protons are created. An obvious possibility is the isomerization of VIIIb to the enamide IXb. This was confirmed in the case of IIIa which, on standing with 2 equiv of dimethylsodium, afforded IXa. Its structure was established by analysis, spectra, and hydrolysis to the known vanillyl ketone Xa and acetamide.

Under more normal racemization conditions, such as run 20, this side reaction is negligible, since the total yield of ketone Xa after hydrolysis in aqueous acid, which includes not only IXa but also any Xa which may have been directly formed, is less than 1%.

## Experimental Section<sup>7</sup>

**Reagents.**—Dimethyl sulfoxide (Matheson Coleman and Bell) was kept over molecular sieves. The water content never exceeded *ca.* 0.05% by Karl Fischer titration. Redistilled DMSO, kept over sieves, was used for the kinetic measurements.

Sodium cyanide was reagent grade, 98.9% NaCN by Volhard titration, 96.5% alkali (as NaCN) by HCl titration using phenol red (pH 7.0).  $\alpha$ -Acetamido- $\alpha$ -vanillylpropionitrile IIIa<sup>2</sup> had mp (*dl*) 176–178°, (*d* or *l*) 202–204° (the *dl* form is a mixture, not a compound); rotation values are 578 m $\mu$ , 43.1°; 546, 49.6; 436, 93.4; 405, 117.5; 365, 167.3. It was recrystallized from methanol for the kinetic work.

$\alpha$ -Acetamido- $\alpha$ -veratrylpropionitrile IIIb had mp (*d*) 142–144°, (*dl*) 142–143° (the *dl* form is a compound); rotation values are 578 m $\mu$ , 36.8°; 546, 42.6; 436, 79.7; 405, 99.6; 365, 141.2. For the kinetics it was recrystallized from benzene-hexane.

Optical rotations were determined on a Zeiss polarimeter at 578, 546, 436, 405, and 365 m $\mu$ . All were 1% in methanol at 30° and all showed correct ORD's for known materials, except as noted.

Infrared spectra were determined on a Perkin-Elmer Model 137 Infracord.

**Racemization of  $\alpha$ -Acetamido- $\alpha$ -vanillylpropionitrile (IIIa) at 160° Using 0.5 Mole of NaCN.**—A mixture of 0.5061 g of *d*-IIIa (0.00204 mole), 0.0502 g of NaCN (0.001 mole), and 2.0 ml of DMSO was warmed until solution was complete, purged thoroughly with nitrogen, and heated with stirring for 10 min in an oil bath at 160°. Most of the solvent was then removed at *ca.* 50° at 1.5 mm. The residue was diluted with 20 ml of water, acidified with HCl, and chilled 0.5 hr. The crystalline precipitate was filtered, washed twice with cold isopropyl alcohol, and once with petroleum ether (30–60°), and dried to give 0.4268 g (84.3%). The optical purity was 40%.

From the mother liquor was obtained a second crop of racemic IIIa, 0.0472 g. Thus the total recovery was 93.6% and the average optical purity 36%.

In another run using the same proportions of reagents but half as much DMSO (1.5 min at reflux, 189°; yield 96% in two crops), the aqueous mother liquor was analyzed, after standing acidified overnight, for ketone. Six chloroform extracts were combined, dried with  $\text{MgSO}_4$ , filtered, stripped, and made accurately to volume. Quantitative vpc comparison with pure Xa solution established that the yield of ketone was only 0.84%.

**Racemization of IIIa Using 0.5 Mole of NaCN and 1 Mole of HCN.**—Optically pure  $\alpha$ -acetamido- $\alpha$ -vanillylpropionitrile IIIa (0.5042 g, 0.002 mole), and 0.0499 g (0.001 mole) of NaCN were dissolved in 2.0 ml of DMSO which was 1.07 N in HCN (0.002 mole). After purging with nitrogen, the mixture was stirred and heated for 10 min in an oil bath at 160°. A strong red color developed.

The reaction was worked up as before, affording 0.4198 g (83.4%) of recovered IIIa, mp 174–198°, whose optical purity was 64%.

**Preparation of Optically Active  $\alpha$ -Acetamido- $\alpha$ -veratryl propionitrile (IIIb).**—Sodium hydride (0.96 g, 50% in mineral oil, 0.02 mole) was washed three times with hexane and brought together with 4.96 g (0.02 mole) of *d*-IIIa in a mixture of 50 ml of dioxane and 15 ml of DMSO. The reaction was allowed to proceed mainly at room temperature and was completed by brief warming.

To the cooled reaction mixture was added 1.89 ml (0.02 mole) of dimethyl sulfate; heat was briefly evolved. It was then heated 10 min on the steam bath, cooled, and stripped under vacuum at *ca.* 1 mm. An oil separated upon addition of 200 ml of water which was extracted four times with methylene chloride. The extracts were washed three times with water, dried with  $\text{MgSO}_4$ , filtered, and evaporated under vacuum, leaving 5.58 g of oil which was crystallized from benzene. The product was filtered, washed with benzene-petroleum ether, and dried to yield 4.36 g (83.3%), mp 139–144°. The mixture melting point with *dl*-IIIb (mp 142–143°) was 134–140°. The ir spectra of *d*- and *dl*-IIIb were identical as chloroform solutions but not as Nujol mulls. The preparation of *dl*-IIIb had previ-

(6) For an example of a similar phenomenon but with a different explanation, see C. A. Kingsbury, *J. Org. Chem.*, **29**, 3262 (1964).

(7) Melting points are uncorrected. Nmr spectra were by courtesy of Drs. N. R. Trenner and B. A. Arison and microanalyses were by R. N. Boos and associates.

ously been carried out in the same way. The ir spectrum was in accord with the structure.

*Anal.* Calcd for  $C_{14}H_{13}N_2O_3$ : C, 64.10; H, 6.92; N, 10.68. Found: C, 63.99; H, 6.93; N, 10.53.

**Racemization of  $\alpha$ -Acetamido- $\alpha$ -veratrylpropionitrile (IIIb) with 0.5 Mole of NaCN.**—To 2.0 ml of DMSO were added 0.5305 g (0.002 mole) of *d*-IIIb and 0.0517 g (0.001 mole) of NaCN. These were dissolved, and the mixture was purged with nitrogen and heated 10 min at 160°. After vacuum distillation of the solvent, the residue was diluted with water and extracted four times with chloroform. The combined extracts were dried with  $MgSO_4$ , filtered, and stripped, and the residue was crystallized from benzene, filtered, washed with benzene-petroleum ether, and dried to give 0.4865 g, 91.6% recovery. This was pure racemic IIIb, rotation 0.00°.

**Preparation of IV (N-Methyl)- $\alpha$ -acetamido- $\alpha$ -veratrylpropionitrile.**—To a cooled and stirred solution of 7.44 g of *dl*-IIIa (0.03 mole) in 90 ml of DMSO was added, first a slurry of NaH (from 2.88 g of 50% NaH, 0.06 mole, which had been washed three times with hexane) in 10 ml of DMSO, and then 5.67 ml (0.06 mole) of dimethyl sulfate. After 0.5 hr, glacial acetic acid was added until the mixture was neutral, the solvent was stripped at 1 mm, and 100 ml of benzene was added. The mixture, which formed two layers, was washed with three 10-ml portions of water, dried with  $MgSO_4$ , filtered, and stripped. The product was crystallized from 1:1 benzene-cyclohexane, filtered, washed, and dried to yield 5.95 g (71.7%). After recrystallization the melting point was 101–103°; ir and nmr spectra were correct.

*Anal.* Calcd for  $C_{15}H_{20}N_2O_3$ : C, 65.19; H, 7.30; N, 10.14. Found: C, 65.49; H, 7.18; N, 9.96.

A sample of *l*-IV, prepared in the same way, had the same ir as the *dl* modification in chloroform but a slightly different one in Nujol, mp 99–105° and mmp ca. 90–100°. Rotation values were 578  $m\mu$ ,  $-41.5^\circ$ ; 546,  $-47.2$ ; 436,  $-82.9$ ; 405,  $-101.6$ ; 365,  $-133.4$ .

**Cyclization of IV to VI.**—A sample of IV was prepared as above from 7.44 g of *l*-IIIa. After addition of the dimethyl sulfate the reaction mixture was aged overnight at room temperature and heated briefly at about 50°; the solvent was removed under vacuum. The solution was strongly alkaline throughout.

The residue was treated with 200 ml of water and extracted ten times with chloroform. The extracts were washed with aqueous KOH, dried with  $MgSO_4$ , filtered, and evaporated. The residue, which crystallized readily, was recrystallized from benzene-cyclohexane, affording 5.38 g (72.3%) of VI, mp 200–207°. After recrystallization from chloroform-benzene, it exhibited the following properties: ir (Nujol), multiple bands at ca. 2.9, 6.01 (w), 6.13 (s), and 6.24  $\mu$  (w), plus other bands (8.60, 8.78, 9.75  $\mu$ ) typical of the veratryl system (no other carbonyl absorption); uv (MeOH),  $\lambda_{max}$  271  $m\mu$  ( $E$  341); nmr ( $CDCl_3$ ),  $\tau$  3.32 (Ar), 5.75 (HC=), 5.48 (NH<sub>2</sub>), 6.22 (OCH<sub>3</sub>), 7.14 (NCH<sub>3</sub>), 7.17 (ArCH<sub>2</sub>), 8.63 (CH<sub>3</sub>C); rotation, 578  $m\mu$  (12.6°), 546 (12.3), 436 (0.0), 405 ( $-15.8$ ), 365 ( $-72.7$ ).

*Anal.* Calcd for  $C_{15}H_{20}N_2O_3$ : C, 65.19; H, 7.30; N, 10.14. Found: C, 64.91; H, 7.35; N, 9.70.

**Hydrolysis of VI to VII.**—Compound VI (0.1166 g) was heated on the steam bath with 10 ml of water and 1 drop of HCl. The pH rose from 3 to 7 over 1 min. Heating another minute with a second drop of HCl did not raise the pH again. On cooling, the product crystallized and was filtered, washed, and dried to yield 0.0406 g; mp 148–150°; ir ( $CHCl_3$ ), 5.67 (m), 5.95 (s), nothing below 3.3  $\mu$ ; nmr ( $CDCl_3$ ),  $\tau$  3.21, 3.35, 3.46, 3.59 (Ar), 6.18 (OCH<sub>3</sub>), 6.96 (NCH<sub>3</sub>), 7.10 (=CCH<sub>2</sub>C=), 7.49, 7.86 with possibly 7.10, 8.23 (ArCH<sub>2</sub>), 8.56 (CH<sub>3</sub>C).

*Anal.* Calcd for  $C_{15}H_{19}O_4N$ : C, 64.96; H, 6.91; N, 5.05. Found: C, 64.50; H, 7.02; N, 5.10.

**Attempted Racemization of IV.**—A solution of 0.5527 g of *l*-IV (0.002 mole) and 0.0487 g of NaCN (0.001 mole) in 2.0 ml of DMSO was heated under nitrogen for 10 min at 160° (touched 170° briefly). The mixture was cooled, neutralized with AcOH, diluted with 20 ml of benzene, washed with three 3-ml portions of water, dried with  $MgSO_4$ , filtered, and stripped under vacuum. The residue (0.55 g of oil) was crystallized from benzene-cyclohexane, taking two crops of IV, 0.3118 and 0.0509 g (total 0.3627 g, 65.7%). These were 99 and 96% optically pure, respectively, with ORD's identical with that of pure IV. As a duplicate run on *dl*-IV gave VI in 18% yield in addition to recovered IV, the yield of recovered *l*-IV above, corrected for this amount of cyclization, is 80%.

**Racemization of IIIa with Radioactive Cyanide.**—A solution of 0.4968 g of optically pure IIIa (0.002 mole) and 0.0492 g (0.001 mole) of NaCN labeled with  $C^{14}$  (64,300 cpm/mg or 3,153,000 cpm/mole) in 2.0 ml of DMSO was heated under nitrogen for 10 min at 150°. The solution was cooled, stripped under vacuum (not over ca. 35°), diluted with water, acidified with HCl, and chilled. The product was filtered, washed successively with cold water and isopropyl alcohol, and dried to yield 0.4490 g (90.4%).

To remove any possible trace of cyanide ion, the product was dissolved in warm methanol, acidified with a trace of HCl, and stripped under vacuum. The residue was redissolved and stripped again. The product was dried and showed 82.2% optical purity. Its radioactivity was 483,000 cpm/mole, 15.3% of that of the starting NaCN.

**Kinetic Experiments.**—The sealed-tube runs (K1–K8) were done in tubes 180 mm long, 2 mm i.d., filled to 120 mm (ca. 0.6 ml), unpurged, with DMSO as the solvent. They were held over refluxing liquid in a specially constructed apparatus in which they were immersed in the vapor and could not touch either the side walls or the condensate return. Temperature was measured by Anschutz thermometers, fully immersed with the tubes. Within each run, good temperature constancy was obtained (within 0.1°), but temperatures could not be maintained from day to day owing to variations in the atmospheric pressure. Readings were obtained by acidifying with acetic acid to pH 5.5–6.0, diluting to 10.00 ml with methanol, and reading the rotation at 30.0° at all five wavelengths in the Zeiss polarimeter. Some samples had a slight yellow cast from oxidation in the upper 2–3 mm of the solution in the sealed tubes and could only be read at the higher 3–4 wavelengths; none gave less than two secure readings, and in all cases the ORD's were identical with that of the starting material. All runs gave good linear semilog plots, except as noted, and duplication of identical tubes was very close.

The results are presented in Tables II–III, and for the sake of brevity only one run will be described in detail, no. K2, for which acetic anhydride was used as the refluxing solvent (see Table V); in other runs, *n*-octane, chlorobenzene, 1-butanol

TABLE V  
DATA FOR RUN K2

Time, hr	Net wt, g	% optical purity
0	0.5791	100.00 <sup>a</sup>
1	0.5897	82.7 $\pm$ 0.4
2	0.5698	70.0 $\pm$ 0.2
4	0.5648	49.5 $\pm$ 0.5
6	0.5616	35.4 $\pm$ 0.3

<sup>a</sup> An unheated tube served as reference point for the run; its rotation was 98.5  $\pm$  0.2% of the value calculated for pure IIIa, reflecting the slight effect of the ca. 2.4% DMSO in the methanol.

and toluene were also employed. The stock solution, whose total volume was 10.00 ml, contained 2.0238 g of IIIa and 0.0402 g of NaCN, total weight 11.1966 g.

Calculation of  $k_2$ 's required a knowledge of the expansion of the reaction mixture with temperature. This was measured at various temperatures for pure DMSO and for several of the stock solutions, and all were about the same. The expansion factors were 110°, 1.07; 117°, 1.08; 139°, 1.11; 131°, 1.10 (calculated).

Run K4 was linear through the first four points (4 hr), and then showed a slight diminution in rate. Run K7 was so fast that only one experimental point, in addition to the zero point, could be obtained.

Runs K7 and K8 were done with a stock solution containing 1.9807 g of IIIa and 0.4235 g of NaCN. These were dissolved in ca. 10 ml of DMSO and stripped at ca. 0.5 mm below 50° to a syrup. This was repeated, the syrup made up to 10.00 ml (net weight 11.2896 g), and the normal procedure followed henceforth.

For the dimethylsodium runs, K13–K16, the reagent was prepared and titrated daily by dissolving 4.8 g of 50% NaH (washed four times with hexane) in 75 ml of DMSO under nitrogen at 58°. Normalities ranged from 1.50 to 1.57. A 2% molar excess of dimethylsodium was used in all runs to take care

of possible errors in titration and transfer of the somewhat viscous reagent. The reaction vessel was a 10-ml volumetric flask with a lengthened neck, which was suspended in a water bath controlled to  $\pm 0.02^\circ$ . Temperature was read with an NBS certified thermometer. Since racemization began at room temperature immediately upon mixing the reagents, the first sample, withdrawn after 30 min in the bath, was taken as zero time. Samples were taken in 1-ml pipets and discharged into 10-ml volumetric flasks containing a freshly prepared mixture of 2 ml of methanol and sufficient acetic acid to be slightly in excess (0.10 ml for K13 and K16, 0.05 ml for K14). These were filled to the mark with methanol and read as before.

The data for one run, K14 (see Table VI), are given. The stock solution, (total volume, 10.00 ml) contained 1.0549 g of IIIb and 2.71 ml of 1.50 *N* dimethylsodium.

TABLE VI  
DATA FOR RUN K14

Time, hr	% optical purity
0.0	100
0.72	87.5 $\pm$ 0.4
1.25	80.2 $\pm$ 0.2
1.97	73.5 $\pm$ 0.5
3.07	65.6 $\pm$ 0.4
4.48	58.6 $\pm$ 0.3

**Volatility of HCN in Racemization Mixtures.**—A solution of 2.00 g (0.00806 mole) of IIIa and 0.1912 g (0.00378 mole) of NaCN in 4 ml of DMSO was partially stripped at 0.5 mm to a net weight of 5.0701 g. A sample of 1.0604 g (20.9%) of this mixture was titrated for cyanide by the Volhard method, and contained 0.000132 mole, or 16.7% of the original amount. Another sample (3.9291 g, 77.5%) was diluted with 15 ml of DMSO and then stripped thoroughly at 50° (0.5 mm). The residue contained 0.0001034 mole of cyanide, or 3.53% of the original amount.

In another experiment, a similar solution was subjected, at 60°, five times alternately to 0.1 atm for 5 sec and then nitrogen at 1 atm. After this treatment the solution was found to contain  $100 \pm 1\%$  of the original charge of cyanide.

This experiment was performed in order to demonstrate that nitrogen purging, or lack of it, did not affect the relative rates of the various reactions described in this paper.

**Isolation of Enamide IXa.**—A solution of 2.48 g of IIIa (0.01 mole) in 10 ml of DMSO was treated with 13.30 ml of 1.52 *N* dimethylsodium (0.202 mole). The solution was stored at 25° for 4 days. Then 1.16 ml (0.202 mole) of acetic acid and 50 ml of water were added, but no IIIa precipitated, even after seeding and cooling. After further dilution with 25 ml of water, the mixture was extracted four times with methylene chloride, and the extracts dried with MgSO<sub>4</sub>, filtered, and evaporated, leaving an oil which crystallized to give 1.26 g. After two recrystallizations from isopropyl alcohol, the melting point was 152–155°. The product had no optical activity. Ultraviolet bands are at  $\lambda_{\max}$  271 m $\mu$  (*E* 659); ir (CHCl<sub>3</sub>) bands are OH at 2.8 and 2.9, C=O and C=C at 5.97 (s) and *ca.* 6.05  $\mu$  (shoulder), respectively. Nmr data was in accord with the structure.

*Anal.* Calcd for C<sub>12</sub>H<sub>15</sub>O<sub>3</sub>N: C, 65.1; H, 6.83; N, 6.34. Found: C, 65.30; H, 7.18; N, 6.43.

A few milligrams of IXa was heated on the steam bath for 10 min with a few drops of water containing a trace of HCl; it dissolved slowly. After removal of the water under vacuum, the residue was taken up in chloroform, dried with MgSO<sub>4</sub>, filtered, and stripped. The ir spectrum of the resulting oil matched a mixture of 3-methoxy-4-hydroxyphenylacetone Xa and acetamide. Analysis by vpc of this oil also showed the presence of these two substances in *ca.* equimolar amounts.

The recrystallization mother liquors of IXa above were chromatographed by the "dry column" technique on silica gel G (E. Merck), developing and eluting with 4:1 chloroform-acetone, affording more single-spot, though somewhat gummy, material whose *R<sub>f</sub>* was the same as that of IXa. The oily component went readily into benzene, in which IXa is insoluble, and its ir spectrum was so similar to that of IXa that it was apparently the other *cis,trans* isomer. This conjecture was supported by hydrolysis in aqueous acid by the above procedure, which produced the same mixture of ketone and acetamide.

**Registry No.**—*dl*-IIIa, 14818-97-4; *dl*-IIIb, 15188-49-5; *dl*-IIIc, 15188-50-8; *dl*-IIId, 7754-92-9; *dl*-IV, 15158-48-2; *l*-IV, 15158-49-3; *dl*-Va, 15158-50-6; *dl*-Vb, 15158-51-7; VI, 15158-52-8; VII, 15158-53-9; IXa, 15158-54-0.