The Stereochemistry of Conjugate Additions. A Study of the Addition of Amines to (2-Nitropropenyl)-benzene

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Pairs of diastereoisomeric dl-1-amino-2-nitro-1-phenylpropanes (IIa and IIb) were obtained when the secondary amines morpholine, piperidine or pyrrolidine underwent addition to (2-nitropropenyl)-benzene (I). The adducts were reduced to the corresponding 1-morpholino-, 1-piperidino- or 1-pyrrolidino-2-amino-1-phenylpropanes (Va and Vb). Results obtained when two of these pairs of diamines (the pairs of morpholino and piperidino compounds) were treated with nitrous acid permitted assignment of the erythro (Va) and threo (Vb) configurations to the individual diamines and to the amino nitro compounds (IIa and IIb) from which they were obtained. Evidence of the threo configuration (Vb) was the formation of hydratropaldehyde in the nitrous acid reaction; evidence of the erythro configuration (Va), the formation of propiophenone. The erythro forms (IIa) of the amine adducts appeared to be less stable than the corresponding threo forms (IIb) and to be formed more rapidly from a presumed common intermediate of the aci-nitro type. The influence of steric hindrance on the α-carbon protonation of chelated forms of the aci-nitro intermediates is suggested as an explanation of the kinetically favored initial formation of the erythro compounds (IIa). A possible correlation of these results with the stereochemistry of reactions of iodine–amine complexes with unsaturated compounds[2] is also discussed. Only a threo adduct (IIb) has thus far been obtained in the addition of the dimethylamine to (2-nitropropenyl)-benzene (I). Likewise, in the addition of the primary amines benzylamine and cyclohexylamine to (2-nitropropenyl)-benzene (I), only one racemic form of the adduct IV was obtained from each amine. All three of these adducts were reduced to the corresponding diamines but the configurations of the latter two were not investigated.

Iodine–amine complexes have been shown to react in a stereospecific fashion with a number of unsaturated compounds.[2] The compounds which react with these reagents are of types which are also capable of undergoing conjugate addition of primary or secondary amines. In seeking an understanding of the mechanism and the stereospecificity of the halogen–amine reactions we have been led to undertake an examination of the addition of amines to (2-nitropropenyl)-benzene (I). The resulting adducts, the 1-amino-2-nitro-1-phenylpropanes, would contain two asymmetric carbon

to learn whether some kind of stereospecificity does, in fact, prevail in conjugate additions of this type and, by determining the relative configurations of the two asymmetric centers formed, the nature and possible explanation of any such stereospecificity.

We have found that when (2-nitropropenyl)-benzene (I) is treated with morpholine, piperidine or pyrrolidine under suitable conditions, the adducts can be obtained as mixtures of diastereoisomers (IIa and IIb) which can be separated by means of fractional crystallization. Good yields
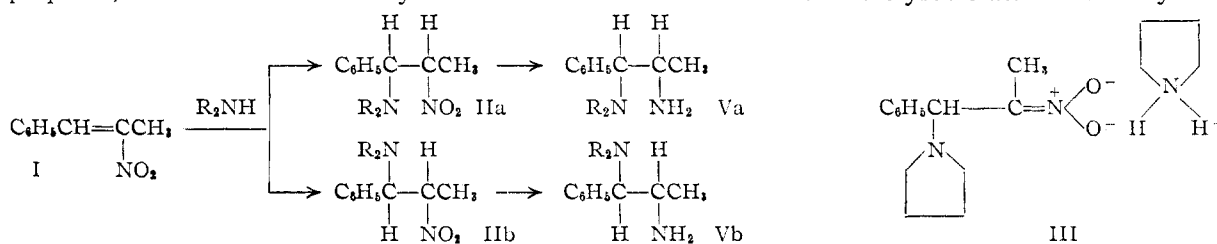
atoms, and would therefore theoretically be capable of existing in two diastereoisomeric racemic forms, each of which is represented here by the formula of one enantiomorph (IIa or IIb). However, although the addition of amines to α,β-unsaturated nitro compounds is well known, we have been able to find no record in the literature of the formation of more than one member of the pair of diastereoisomeric racemates which should exist in the case of many of such adducts.[3] It was our first objective

(70–95%) of the adducts were formed, but separation of the pure diastereoisomers was sometimes difficult. In the case of all three of the amines, when the addition reactions were conducted between equimolecular amounts of the amine and the nitroölefin in petroleum ether, or in benzene–petroleum ether mixtures, the form now considered to have the erythro configuration (IIa) predominated in the initial crystalline precipitate. On the other hand, from reaction mixtures produced when an excess of the amine was used, or when the addition was conducted in ethanol, usually only the threo isomer (IIb) could be separated in the pure form, presumably because these conditions permitted the approach to a state of equilibrium in which the threo isomer was largely predominant. The erythro isomers (IIa) were observed to be unstable with respect to conversion into threo isomers (IIb) when attempts were made to recrystallize them from ethanol. In the case of pyrrolidine it was possible, by conducting the reaction in ethyl ether and using two moles of pyrrolidine to one of (2-nitropropenyl)-benzene (I), to obtain an adduct

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(2) (a) P. L. Southwick and D. R. Christman, THIS JOURNAL, 74, 1886 (1952); (b) 75, 629 (1953); (c) N. H. Cromwell and R. J. Mohrbacher, ibid., 75, 6252 (1953); (d) N. H. Cromwell, R. P. Cahoy, W. E. Franklin and G. D. Mercer, ibid., 79, 922 (1957).

(3) Reactions in which diastereoisomeric products might in theory have been obtained by the addition of ammonia or amines to α,β-unsaturated nitro compounds are described in the following references: (a) D. E. Worrall, THIS JOURNAL, 43, 919 (1921); (b) 60, 2841 (1938); (c) D. E. Worrall and J. Finkel, ibid., 61, 2969 (1939); (d) J. Loevenich and H. Gerber, Ber., 63, 1707 (1930); (e) J. Loevenich, J. Koch and U. Puchnot, ibid., 63, 636 (1930); (f) R. L. Heath and J. D. Rose, J. Chem. Soc., 1486 (1947).

as a crystalline, water-soluble pyrrolidinium salt of the *aci*-nitro form (III).
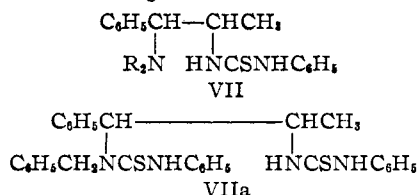
The addition of dimethylamine to (2-nitropropenyl)-benzene (I) was attempted only in a solution containing ethanol and yielded the *threo* form of the adduct (IIb) under these conditions. It was also possible to obtain adducts (IV) with the primary amines cyclohexylamine and benzylamine by means of a procedure which involved the precipitation of these products from the reaction mixtures by forming the hydrochlorides. In the cases of both of these amines only one racemic form

$$C_6H_5CH—CHCH_3 \qquad C_6H_5CH—CHCH_3$$
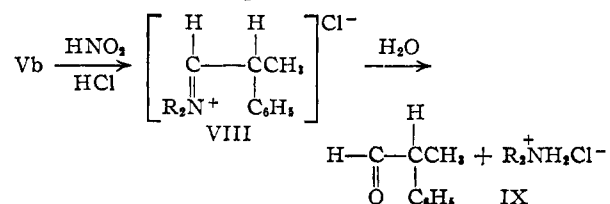$$\text{IV} \quad R\dot{N}H \quad \dot{N}O_2 \qquad \text{VI} \quad R\dot{N}H \quad \dot{N}H_2$$
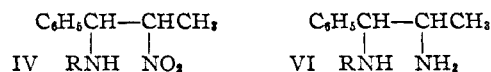
of the adduct was obtained, but the configuration of this form was not determined.

The assignments of the configurations IIa or IIb to the two forms of the adducts obtained with morpholine and piperidine, and to the one form obtained with dimethylamine were based upon the results of experiments in which the diamines Va and Vb, secured by reduction of the adducts, were deamininated and rearranged by the action of nitrous acid. In order to make such experiments meaningful it was necessary to find a method of reducing the nitro group of the adducts in such a way as to leave undisturbed the configuration at carbon 2, the point of attachment of the nitro group. Reduction by use of lithium aluminum hydride, a procedure which had been used previously[2b] with closely related compounds, resulted in the formation of mixtures of diastereoisomeric diamines, presumably due to loss of configurational stability at carbon 2. This result is in agreement with the observations of Kornblum and Fishbein,[4] who recently reported that complete racemization occurs in the reduction of (−)-2-nitroöctane to 2-aminooctane with lithium aluminum hydride. In experiments with *threo* forms of the morpholino and piperidino derivatives (IIb, R₂N− = morpholino or piperidino) a single diamine was obtained when conversion to the diamine was accomplished by hydrogenation over Raney nickel in ethanol solution or, in the case of an experiment with the *threo*-morpholino derivative, by hydrogenation over platinum oxide in glacial acetic acid. Evidently the original configuration of the adducts was retained in these experiments. However, the catalytic hydrogenation methods failed to preserve the configuration when applied to the *erythro* forms IIa. Investigation of other methods of reduction led to the finding that the amino nitro compounds IIa and IIb enjoy a considerable configurational as well as structural stability in concentrated aqueous hydrochloric acid, and that both *threo* and *erythro* forms can be reduced in that medium by use of stannous chloride with little or no interchange of configurations.[5] Each of the amino nitro compounds of the types IIa, IIb and IV were reduced in this manner, and the resulting diamines (Va, Vb or VI) were characterized, either in the form of the free bases, as salts with sulfuric or *p*-

(4) N. Kornblum and L. Fishbein, This Journal, **77**, 6266 (1955).

(5) It is reported (ref. 4) that configurational stability is maintained in the reduction of (−)-2-nitroöctane with iron in glacial acetic acid.

toluenesulfonic acid, or as phenylthiourea derivatives. The benzylamino derivative (VI, R = benzyl) reacted with two moles of phenyl isothiocyanate to give the compound VIIa, but the cyclohexyl derivative (VI, R = cyclohexyl), like the diamines of the types IIa and IIb (which yielded the phenylthiourea derivatives VII), reacted with only one mole of the reagent.

$$C_6H_5CH—CHCH_3$$
$$R_2\dot{N} \quad HN\dot{C}SNHC_6H_5$$
$$\text{VII}$$

$$C_6H_5CH——————CHCH_3$$
$$C_6H_5CH_2N\dot{C}SNHC_6H_5 \quad HN\dot{C}SNHC_6H_5$$
$$\text{VIIa}$$

When those forms of the diamines which have been assigned the *threo* configuration Vb were treated with nitrous acid and the neutral component of the reaction mixtures was treated with semicarbazide, mixtures of the semicarbazones of hydratropaldehyde (IX) and acetophenone were obtained. Before fractional crystallization the infrared spectra of the crude semicarbazones obtained in an experiment with *threo*-morpholino compound contained all of the bands found in the spectrum of hydratropaldehyde semicarbazone and in the spectrum of acetophenone semicarbazone, but no others. The presence of the acetophenone derivative, which represented a considerable proportion of the mixture when the deamination–rearrangements were conducted in 50% acetic acid rather than in aqueous hydrochloric acid, can evidently be ascribed to nitrous acid degradation of hydratropaldehyde (IX), as was demonstrated by experiment. Treatment of hydratropaldehyde with nitrous acid under one of the sets of conditions used in the experiments with the diamines, followed by treatment of the product with semicarbazide, yielded acetophenone semicarbazone. The principal, if not the sole, course of the deamination–rearrangement itself is thus considered to be that represented in the equations

$$Vb \xrightarrow[\text{HCl}]{\text{HNO}_2} \left[\begin{array}{cc} H & H \\ | & | \\ C——CCH_3 \\ \| & | \\ R_2N^+ & C_6H_5 \end{array} \right]^{Cl^-} \xrightarrow{H_2O}$$
$$\text{VIII}$$

$$\underset{\substack{\| \quad | \\ O \quad C_6H_5}}{H—C—CCH_3} + R_2\overset{+}{N}H_2Cl^-$$
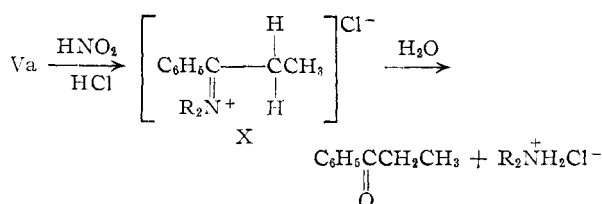$$H \qquad \qquad \text{IX}$$

On the other hand, when diamines now believed to be of the *erythro* configuration were allowed to react with nitrous acid, treatment of the neutral fraction of the reaction mixtures with semicarbazide yielded propiophenone semicarbazone and the derivatives of hydratropaldehyde and acetophenone appeared to be absent. Thus the deamination–rearrangement of the *erythro*-diamines Va evidently involved hydrogen rather than phenyl migration as shown.

The postulated hydrogen migration should be promoted by electron donation from the morpholino nitrogen, and it seems unlikely that much of the propiophenone could result from hydrolysis of an enamine such as (1-morpholinopropenyl)-ben-
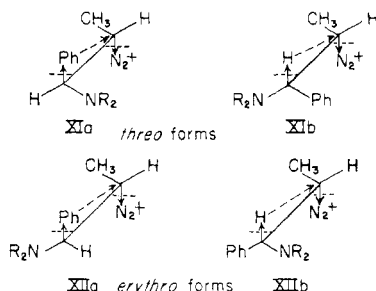
zene, which would be formed if decomposition of the diazonium salt should lead to proton elimination from carbon 1.

$$\text{Va} \xrightarrow[\text{HCl}]{\text{HNO}_2} \left[\begin{array}{c} \text{H} \\ | \\ \text{C}_6\text{H}_5\text{C}\underset{\underset{\text{R}_2\overset{+}{\text{N}}}{\|}}{\overset{}{\quad}}\overset{|}{\underset{\text{H}}{\text{CCH}_3}} \\ \end{array} \right]^{\!\!\text{Cl}^-} \xrightarrow{\text{H}_2\text{O}}$$
$$\qquad\qquad\qquad\qquad X$$
$$\underset{\text{O}}{\overset{\|}{\text{C}_6\text{H}_5\text{CCH}_2\text{CH}_3}} + \text{R}_2\overset{+}{\text{N}}\text{H}_2\text{Cl}^-$$

By utilizing assumptions which Curtin and his associates[6] have shown to be valid for interpreting the results of the similar deamination–rearrangement reactions of a number of α,α-diaryl-β-amino alcohols it has been possible to assign configurations to the diamines Va and Vb on the basis of the nitrous acid reactions. It is assumed that phenyl migration and hydrogen migration, which lead to hydratropaldehyde and propiophenone, respectively, proceed *via* transition states in which the migrating group or atom makes its new attachment on the side of carbon 2 opposite that from which the nitrogen of the intermediate diazonium ion is simultaneously making its departure.[7] Hence, transition states for phenyl and hydrogen migration in the *threo* forms would be represented by the diagrams XIa and XIb, respectively, and in the *erythro* forms by the diagrams XIIa and XIIb, respectively.[8] It is further assumed that, other things being equal, the favored migration

XIa   *threo* forms   XIb

XIIa   *erythro* forms   XIIb

will be that which involves the minimum of steric interaction in the transition state of groups on carbon 1 with groups on carbon 2. Of the transition states for phenyl migration (XIa and XIIa) that derived from the *threo* isomer (XIa) is clearly the more favorable, for it separates the bulky sub-

stituted amino group, R_2N, from methyl, whereas XIIa places these groups in a position to interact. Thus it seems safe to assume that those diamines (V) which yield hydratropaldehyde have the *threo* configuration[9a]; it should also be noted that in the diazonium intermediates of the *threo* configuration, steric interactions between groups should favor a high population for the conformation which leads directly to the transition state for phenyl migration (XIa), and should therefore exert a steric effect more favorable to phenyl migration than to hydrogen migration.[9b]
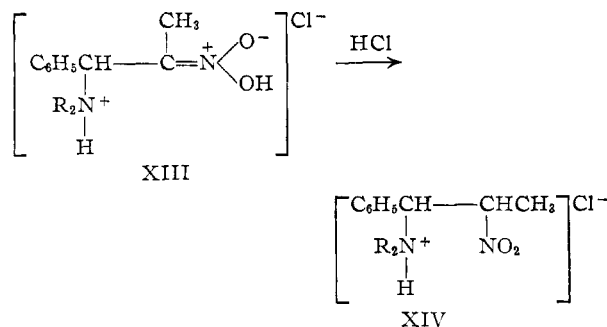
It then follows that the other member of each pair of diastereoisomeric diamines, the one which in each instance yielded propiophenone as the deamination–rearrangement product, is of the *erythro* configuration, and that of the two transition states for hydrogen migration (XIb and XIIb) those (XIIb) derived from *erythro* forms must have been the more favorable. Presumably this signifies that there is less interaction between neighboring methyl and phenyl groups in XIIb than between neighboring methyl and R_2N in XIb. Such would certainly be the case if in the transition state of the rearrangements formation of the carbon–nitrogen double bond leading to the presumed intermediate X has progressed to the point of making it necessary for the substituents on the amino nitrogen to approach the plane defined by carbons 1 and 2 and the amino nitrogen. For although in XIIb interaction between phenyl and methyl can be minimized by rotation of phenyl, the lack of free rotation about the developing carbon–nitrogen double bond would have the effect of forcing the substituents R (methylene groups of the heterocyclic rings in the present cases) into strong interaction with the methyl group in the case of transition states XIIa and XIb, and could account for the apparent failure of these states to contribute to the reactions.

A more detailed study than has thus far been attempted should be made of the conditions which control the configuration which is produced in the addition of the amines to (2-nitropropenyl)-benzene (I). However, there are a number of indications from the present work that the *erythro* forms are produced more rapidly than the *threo* forms, and that the *threo* forms are easily secured only because they are favored in the equilibrium between the forms which is reached under appropriate conditions. It already has been mentioned that the *erythro* forms separated from solution first when the compounds were prepared in benzene–petroleum ether mixtures. This result could, of course, have been determined in part by relative solubilities and rates of crystallization, and is not necessarily a reliable indication that the *erythro* forms are actually produced more rapidly than the *threo* forms in the addition process.[10] However, rather more substantial evidence pointing to the same conclu-

(6) (a) P. I. Pollack and D. Y. Curtin, THIS JOURNAL, **72**, 961 (1950); (b) D. Y. Curtin and P. I. Pollack, *ibid.*, **73**, 992 (1951); (c) D. Y. Curtin, E. E. Harris and P. I. Pollack, *ibid.*, **73**, 3453 (1951); (d) D. Y. Curtin and M. C. Crew, *ibid.*, **77**, 354 (1955).

(7) Most recent investigators of similar rearrangements have favored the view that it is the diazonium ion which undergoes rearrangement. B. M. Benjamin and C. J. Collins, THIS JOURNAL, **78**, 4952 (1956), list references concerning the nature of the amine–nitrous acid reaction and of the rearrangement process. Very recently D. J. Cram and J. E. McCarty, *ibid.*, **79**, 2866 (1957), and A. Streitwieser and W. D. Schaeffer, *ibid.*, **79**, 2888 (1957), have discussed the mechanisms of rearrangements and other reactions undergone by alkyldiazonium ions. However, the same conclusions regarding configuration would follow from an interpretation of the present results on the basis of a process such as the cyclic molecular rearrangement of a diazo-hydroxide pictured by P. S. Bailey and J. G. Burr, *ibid.*, **75**, 2951 (1953).

(8) In these diagrams solid arrows crossed by a dotted line show the breaking of a bond by a shift of electrons in the indicated direction. Dotted arrows indicate formation of a new bond.

(9) (a) This would be one of the expected manifestations of the "*cis* effect." See D. Y. Curtin, *Record Chem. Progress*, (*Kresge Hooker Sci. Lib.*), **15**, 111 (1954). The *cis* effect would presumably be quite large in the present instance. (b) *Cf.* D. J. Cram and J. E. McCarty, THIS JOURNAL, **79**, 2866 (1957).

(10) N. H. Cromwell and R. A. Setterquist, *ibid.*, **76**, 5752 (1954), have recently investigated a case in which solubility relationships may have an important effect on the position of equilibrium between diastereoisomers which are interconvertible by enolization.

sion was found in the demonstration that conversion of the protonated *aci*-nitro form (the salt XIII) to the protonated amino nitro compound (the salt XIV) in aqueous hydrochloric acid (in which there is no apparent interconversion of configurations) leads very largely to the *erythro* configuration. A solution of *dl-threo*-1-morpholino-2-

$$
\left[\begin{array}{c} CH_3 \\ | \\ C_6H_5CH\!-\!\!-\!C\!\!=\!\!\overset{+}{N}\!\!\big\langle{}^{O^-}_{OH} \\ | \\ R_2\overset{+}{N} \\ | \\ H \end{array} \right] Cl^- \xrightarrow{HCl}
$$

XIII

$$
\left[\begin{array}{c} C_6H_5CH\!-\!\!-\!CHCH_3 \\ | \qquad\quad | \\ R_2\overset{+}{N} \qquad NO_2 \\ | \\ H \end{array} \right] Cl^-
$$

XIV

nitro-1-phenylpropane (IIb, R_2N = morpholino) in aqueous sodium hydroxide was prepared. Such a solution must contain the sodium salt of the *aci*-nitro form of the compound, which cannot exist in diastereoisomeric configurations.[11] When the solution was poured into an excess of 20% aqueous hydrochloric acid and the mixture was allowed to stand for 24 hours to complete the conversion into the nitro form, it was the *erythro* configuration of the compound which was isolated following neutralization of the solution and use of an isolation procedure involving ether extraction and precipitation of the hydrochloride of the compound from the ether extract.[12]

Nitrous acid reactions have not as yet been carried out on those diamines Va and Vb in which R_2N is the pyrrolidino group, but configurations for the two pyrrolidino adducts (IIa and IIb, R_2N = pyrrolidino) have been assigned tentatively on the assumption that the less stable, more rapidly formed isomer is the *erythro* compound. It is worthy of note in this connection that when the pyrrolidinium salt of the *aci*-nitro form of 1-pyrrolidino-2-nitro-1-phenylpropane (III) was dissolved in concentrated hydrochloric acid and then reduced with stannous chloride, only the assumed *erythro* form of *dl*-1-pyrrolidino-2-amino-1-phenylpropane (Va, R_2N = pyrrolidino) was obtained.

Chelated *aci*-nitro forms XV of the amino nitro compounds IIa or IIb would be the initial products of the amine addition to the unsaturated nitro compound I if such addition proceeded in the 1,4-manner by a bimolecular (quasi six-ring) process, as has been suggested previously by Cromwell and Cram[13] for the conjugate addition of amines to α,β-unsaturated ketones. The experiments just

(11) N. Kornblum, N. H. Lichtin, J. T. Patton and D. C. Iffland, THIS JOURNAL, **69**, 307 (1947).

(12) The indications from recent experiments on a larger scale performed by J. R. Stemniski in this Laboratory are that when the 1-morpholino-2-nitro-1-phenylpropanes (IIa and IIb, R_2N = morpholino) are formed in aqueous hydrochloric acid solution from the hydrochloride of the corresponding *aci*-nitro compound (XIII, R_2N = morpholino) the *erythro-threo* ratio is greater than 3 to 1. The Nef hydrolysis reaction occurred only to a minor extent, if at all.

(13) N. H. Cromwell and D. J. Cram, THIS JOURNAL, **65**, 301 (1943).

described with salts of the *aci*-nitro forms[14] seem to demonstrate that the degree of stereospecificity represented by the observed initial preponderance of the unstable *erythro* forms must be compatible with a mechanism involving *aci*-nitro intermediates.[15] Indeed, if it can be assumed that the chelated condition represents a favored state for the *aci*-nitro forms, it is not difficult to explain why it is the *erythro* form of the adducts (IIa) which is kinetically favored. In the conversion of an *aci*-nitro form in the chelated condition XV into the nitro form IIa or IIb, the attack of a proton donor (here represented as the hydronium ion) at carbon 2 would be less obstructed by the hydrogen at carbon 1 than by the phenyl, and should therefore be expected to accomplish the protonation most frequently from the lower side of the ring as depicted here, the side of the hydrogen atom. If such an influence does operate, it would favor the *erythro*

XV IIa
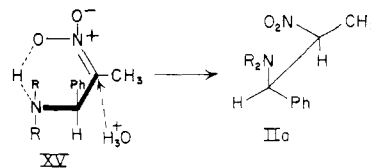
form (IIa), as shown. Recently Zimmerman[16]

(14) Such *aci*-nitro compounds are apparently very unstable in the free form with respect to decomposition into the parent amine and the unsaturated nitro compound I. The derived anions are evidently stable, since the compounds dissolve without decomposition in aqueous sodium hydroxide. The hydrochlorides of the *aci*-nitro compounds (XIII) are evidently stable also, for stable solutions are obtained by adding solutions of the sodium salts of *aci*-nitro forms quickly to an excess of aqueous hydrochloric acid. The instability of the free *aci*-nitro forms is shown by the fact that bringing either a solution of their hydrochlorides XIII in hydrochloric acid or solutions of their sodium salts in sodium hydroxide to the neutral point results in a rapid dissociation into the parent amine and (2-nitropropenyl)-benzene (I) with precipitation of the latter compound from the aqueous solution. On the other hand, the neutralization of acid solutions of the hydrochlorides of the nitro forms (XIV) in aqueous acid results in precipitation of the amino nitro compound IIa or IIb.

(15) The *aci*-nitro forms and their derived anions would, of course, provide a route for the observed interconversion of the diastereoisomeric amino nitro compounds IIa and IIb which occurs in neutral hydroxylic solvents or in non-hydroxylic solvents when excess amine is present. The success of our efforts to obtain the less stable *erythro* forms of three of these compounds in some quantity can be attributed to the facts that (1) the *erythro* forms IIa were kinetically favored in the conversion of the *aci*-nitro forms of the adducts or their anions into the nitro forms, and (2) the adducts could, when desired, be purified substantially in the absence of agents for proton transfer so that the *erythro* forms IIa, once obtained, did not revert rapidly back to the *aci*-nitro forms and thence to the stable *threo* configuration IIb of the nitro forms. Ingold has discussed at length a number of analogous situations concerned with prototropic processes in all of which the less stable tautomer is the one formed most rapidly in the protonation process. See C. K. Ingold, "Structure and Mechanisms in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapter X.

(16) (a) H. E. Zimmerman, THIS JOURNAL, **78**, 1168 (1956); (b) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955). In certain other situations there is evidence that what should be the more stable forms have been kinetically favored in ketonization processes. See observations and theory by Cromwell, *et al.*, ref. 2d. If an attempt is made to extend Cram's rule of "steric control of asymmetric induction" (D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **74**, 5828 (1954)) to α-carbon protonation of these *aci*-nitro compounds initial predominance of the *erythro* forms is predicted only if R_2N- is considered effectively smaller than phenyl. NOTE ADDED IN PROOF: Since this paper was submitted for publication H. E. Zimmerman, T. E. Nevins and B. S. Thyagarajan have reported that in the conversion of the *aci*-nitro form of 1-nitro-2-phenylcyclohexane into the nitro form the less stable *cis*-isomer is favored. See Abstracts of the 132nd Meeting of the American Chemical Society, New York, N. Y., September 8 to 13, 1957, p. 39-P.

has demonstrated that in the ketonization of the enol forms of certain cyclic ketones the preponderant formation of a kinetically favored, less stable diastereoisomer can be explained in a very similar fashion.

A reasonable extension of this interpretation of conjugate amine addition could be used to explain the net *trans* addition which apparently must be assumed[2b,17] in order to account for the preponderant *trans* configuration which has been observed in the ethylenimine ketones produced by the action of mixtures of a primary amine and a primary amine–iodine complex on an α,β-unsaturated ketone of the *trans* configuration.[18,19] Conjugate addition of a primary amine to the ketone would lead to the chelated intermediate XVI, which might be expected to undergo attack by the iodinating agent (here shown as the N-iodo amine RNHI) mainly on the side of the chelate ring away from the substituent R″ on the β-carbon. This would result in an *erythro* configuration for the adduct XVII and hence to the observed *trans*-configuration of the ethylenimine ketone XVIII.[20,21] However, the use of bromine rather than iodine with a pri-

XVI   RN–I   XVII   XVIII
        |
        H
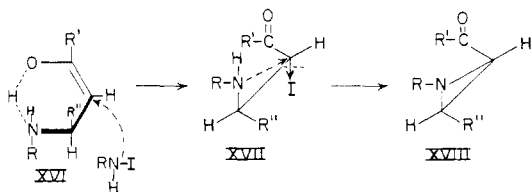
mary amine has led in one instance mainly to a *cis*-ethylenimine ketone,[2d] a result which attests to the probable multiplicity of the factors governing the stereochemistry of reactions involving N-halo primary amines.

Experimental[22]

dl-erythro- and *dl-threo-*1-Morpholino-2-nitro-1-phenylpropane.—A solution of 65.2 g. (0.4 mole) of (2-nitropropenyl)-

(17) N. H. Cromwell and M. A. Graff, *J. Org. Chem.*, **17**, 414 (1952).

(18) Similar experiments with an α,β-unsaturated ketone having the *cis* configuration of substituents on the α,β-double bond are in progress in these laboratories. The reaction mechanism suggested here would require the formation of the *trans*-ethylenimine ketones from the *cis*-α,β-unsaturated ketones also. *trans* addition of the elements of an N-iodamine by a concerted process, as postulated previously,[2b,17] would presumably be expected to lead to a considerable proportion of the *cis*-ethylenimine ketone from a *cis*-α,β-unsaturated ketone.

(19) Predominant *trans* addition also has been observed in the addition of acids to α,β-unsaturated ketones. See (a) W. R. Vaughan, R. L. Craven, R. O. Little, Jr., and A. C. Schoenthaler, THIS JOURNAL, **77**, 1594 (1955), and (b) A. I. Kosak and H. M. Leyland, *J. Org. Chem.*, **21**, 733 (1956).

(20) It is assumed that the ring-closure entails an inversion of configuration at the α-carbon. *Cf.* (a) N. H. Cromwell, G. V. Hudson, R. A. Wankel and P. J. Vanderhorst, THIS JOURNAL, **75**, 5384 (1953); (b) F. H. Dickey, W. Fickett and H. J. Lucas, *ibid.*, **74**, 944 (1952); (c) G. K. Helmkamp and H. J. Lucas, *ibid.*, **74**, 951 (1952).

(21) The stereochemistry of additions of N-halo secondary amines to unsaturated systems (see P. L. Southwick and W. L. Walsh, THIS JOURNAL, **77**, 405 (1955)) is a current subject of investigation in these laboratories. Prof. N. H. Cromwell reports (ref. 2d and private communication) that he is engaged in an extended study of the stereochemistry involved in the formation of ethylenimine ketones *via* additions of primary amines to α-bromo-α,β-unsaturated ketones and of N-haloamines to α,β-unsaturated ketones.

(22) Microanalyses by Drs. G. Weiler and F. B. Strauss, Oxford, England, and Geller Microanalytical Laboratories, West Englewood, N. J. Melting points are corrected.

benzene[23] in 250 ml. of a mixture of two volumes of petroleum ether, b.p. 65–110°, and one volume of benzene was immersed in an ice-bath and 34.8 g. (0.4 mole) of morpholine was added dropwise while the mixture was agitated. After a short period of standing, a first crop of 62 g. of white crystals separated, m.p. 75–85°. By a process involving concentration of mother liquors and systematic fractional recrystallization of the various crops of crystals from the same kind of petroleum ether–benzene solvent mixture, it was possible to separate from a total of 95 g. (a 95% yield) of mixed diastereoisomers 25 g. (a 25% yield) of the *erythro* form, white prisms, m.p. 84–85°, and 23 g. (a 23% yield) of the *threo* form, white prisms, m.p. 141.5–143.5°.

Anal. Calcd. for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found (*erythro* form): C, 62.73; H, 7.45; N, 11.2. Found (*threo* form): C, 62.67; H, 7.11.

dl-erythro- and *dl-threo-*1-Piperidino-2-nitro-1-phenylpropane.—To a solution of 65 g. (0.4 mole) of (2-nitropropenyl)-benzene in 200 ml. of petroleum ether (b.p. 65–110°), 34 g. (0.4 mole) of piperidine was added dropwise while the mixture was agitated and cooled in an ice-bath. A number of crops of crystals totaling 90 g. (90% yield) were obtained by filtering the solution after a short period of standing and then repeatedly concentrating and filtering the mother liquors. Systematic fractional crystallization from a 2:1 benzene–petroleum ether mixture then yielded 23 g. of the *erythro* product as white prisms, m.p. 72–73.5°, and 26 g. of the *threo* product, also as white prisms, m.p. 95–96°.

Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found (*erythro* form): C, 67.62; H, 8.17. Found (*threo* form): C, 67.96; H, 8.10; N, 10.9.

dl-erythro- and *dl-threo-*1-Pyrrolidino-2-nitro-1-phenylpropane.—To a supersaturated solution containing 62 g. (0.38 mole) of (2-nitropropenyl)-benzene (I) dissolved in 150 ml. of petroleum ether (b.p. 65–110°) 27 g. (0.38 mole) of pyrrolidine was added rather rapidly while the mixture was agitated and cooled in an ice-bath at frequent intervals to control the rise in temperature. The mixture was then placed in an ice-bath and the 12 g. of white crystals (m.p. 36–39°) which quickly separated were removed and recrystallized from ether. White leaflets were obtained (7 g., 8% yield), m.p. 38–39°. This is thought to be the *erythro* adduct. After the remainder of the reaction mixture had been allowed to stand for several hours, an additional 62 g. of white crystals, m.p. 79–83°, were removed. This material was recrystallized several times from a 2:1 petroleum ether (b.p. 65–110°)–benzene mixture to yield 33 g. (37% yield) of the presumed *threo* adduct as white prisms, m.p. 85–87°.

Only the *threo* form was stable enough in the free form to be analyzed.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74. Found (*threo* form): C, 66.54; H, 7.53.

A hydrochloride, m.p. 115–116°, which is thought to be mainly that of the *erythro* form was obtained by passing hydrogen chloride into a dry ether solution of the *erythro* adduct and recrystallizing the resulting precipitate from an ethanol–ether mixture. However, analysis showed the carbon content of the sample to be somewhat lower than the calculated value, although the expected results for hydrogen and nitrogen were obtained.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$·HCl: C, 57.67; H, 7.07; N, 10.35. Found: C, 56.02; H, 6.89; N, 10.30.

Pyrrolidinium 1-Pyrrolidino-2-*aci*-nitro-1-phenylpropane. —Pyrrolidine (10.75 g., 0.15 mole) was added dropwise to a solution of 25 g. (0.15 mole) of (2-nitropropenyl)-benzene in 150 ml. of dry ether while the mixture was agitated and cooled in an ice-bath. Shortly after this addition was completed another 10.75 g. of pyrrolidine was added rapidly to the mixture. A white crystalline precipitate (40 g., m.p. 64–68°) separated immediately. Following recrystallization from anhydrous ether, white prisms were obtained, m.p. 71–73°. The yield was 29 g. (62%). This substance, which is freely water-soluble, decomposes, probably by loss of pyrrolidine, unless kept in a stoppered container or refrigerated.

(23) H. B. Hass, A. G. Susie and R. L. Heider, *J. Org. Chem.*, **15**, 8 (1950).

Anal. Calcd. for $C_{13}H_{18}N_2O_2 \cdot C_4H_9N$: C, 66.85; H, 8.90; N, 13.7. Found: C, 66.56; H, 8.78; N, 13.2.

The compound also was obtained by addition of an equivalent of pyrrolidine to an ethereal solution of either the *dl-erythro* or *dl-threo* form of 1-pyrrolidino-2-nitro-1-phenylpropane. From the *threo* form the yield was low, probably because conversion to the *aci*-nitro form was slow in this case.

dl-threo-1-Dimethylamino-2-nitro-1-phenylpropane.—A solution of 22.5 g. (0.5 mole) of anhydrous dimethylamine in 75 ml. of absolute ethanol was added slowly to a solution of 82.5 g. (0.506 mole) of (2-nitropropenyl)-benzene in 200 ml. of a 1:1 mixture of benzene and petroleum ether (b.p. 65–110°). After a short period of standing, this solution deposited 62 g. (59.5% yield) of a white precipitate, m.p. 107–111°. After several recrystallizations from the 1:1 benzene–petroleum ether mixture, 47 g. (45% yield) of the *threo* adduct was obtained as white prisms, m.p. 110.5–112.5°.

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74. Found: C, 63.77; H, 7.71.

1-Cyclohexylamino-2-nitro-1-phenylpropane.—To a solution of 33 g. (0.2 mole) of (2-nitropropenyl)-benzene in 150 ml. of anhydrous ether 20 g. (0.2 mole) of cyclohexylamine was added slowly. A short time after the addition was completed, a stream of hydrogen chloride was passed into the solution. A solid precipitate soon began to form, but after a few minutes a gummy material began to separate. At this point the gas flow was interrupted and the solution was filtered to remove 8 g. of a solid, m.p. 170–195°, which proved to be mainly cyclohexylamine hydrochloride. Addition of hydrogen chloride to the filtrate then caused separation of a gummy precipitate which fully solidified when the mixture was allowed to stand. The precipitate was removed by filtration and washed several times with ether. Crystallization from an absolute ethanol–ether solution yielded 30 g. (50%) of white needles, m.p. 132–135°. This proved to be the hydrochloride of 1-cyclohexylamino-2-nitro-1-phenylpropane.

A solution of 10 g. of this product in 100 ml. of water was made slightly alkaline by addition of a 10% aqueous sodium hydroxide solution and extracted three times with ether. The combined ether extracts were washed once with water, dried over Drierite and concentrated under reduced pressure. Recrystallization of the residue several times from petroleum ether (b.p. 65–110°) yielded 3 g. (34%) of 1-cyclohexylamino-2-nitro-1-phenylpropane as small white prisms, m.p. 62–64°.

Anal. Calcd. for $C_{15}H_{21}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.91; H, 8.19; N, 10.8.

Addition of Benzylamine to (2-Nitropropenyl)-benzene.—Benzylamine (21.4 g., 0.2 mole) was added to a solution of 33 g. (0.2 mole) of (2-nitropropenyl)-benzene in 150 ml. of anhydrous ether. Hydrogen chloride was passed into the solution and the initial solid precipitate consisting mainly of benzylamine hydrochloride (10 g.) was removed by filtration. The gummy precipitate obtained by further addition of hydrogen chloride became solid after a period of standing and was recrystallized from an absolute ethanol–ether mixture to give 35 g. (a 58% yield) of white needles, m.p. 135–136°. This product, which was evidently the hydrochloride of 1-benzylamino-2-nitro-1-phenylpropane, was not further characterized except by means of the reduction described below.

Reduction of 1-Amino-1-phenyl-2-nitropropanes (IIa, IIb and IV).—Reduction by stannous chloride in hydrochloric acid solution (procedure A) was used with all of the compounds. When the sample of an amino nitro compound reduced by this procedure consisted of a single diastereoisomer in substantially pure form no difficulty was ever encountered in obtaining the resulting diamine or its derivatives as single diastereoisomers. When, as in reduction with lithium aluminum hydride (procedure C), mixtures of diastereoisomeric diamines were produced, the phenylthiourea derivatives formed with phenyl isothiocyanate melted over a considerable range and could be separated into two components by careful fractional crystallization. Catalytic hydrogenation over Raney nickel or platinum (Adams) catalysts (procedure B) gave a single product with the *threo* isomers that were reduced in this manner, but mixtures of diastereoisomers with *erythro* forms.

Procedure A.—Quantities as well as proportions of materials used were very similar in most of the experiments.

In the cases of the cyclohexyl and benzylamine adducts (IV, R = cyclohexyl or benzyl) and the *erythro*-pyrrolidine adduct (IIa, R_2N = pyrrolidino) the compound to be reduced was added to the stannous chloride–hydrochloric acid solution in the form of the solid hydrochloride, whereas in all other cases the compounds were dissolved in hydrochloric acid and added in solution, as in the standard procedure given below:

A solution of *ca.* 0.08 mole of the amino nitro compound in 75 ml. of concentrated hydrochloric acid was added to a stirred solution of 68.5 g. (0.36 mole) of stannous chloride in 75 ml. of concentrated hydrochloric acid. The rate of addition was controlled so as to maintain the temperature of the mixture at 50–60°. This temperature was maintained by heating for 1 hour after the addition was complete, and the mixture was then poured into 300 ml. of water. The resulting solution was cooled in an ice-bath and neutralized by careful addition of 140 g. (3.5 moles) of sodium hydroxide in a concentrated aqueous solution. The mixture was then extracted four times with 400-ml. portions of ether. The ether extracts were dried over Drierite and concentrated under reduced pressure. The product was then purified by distillation under reduced pressure.

Procedure B.—A solution of 0.08 mole of the amino nitro compound in 150 ml. of absolute ethanol was shaken with 1.0 g. of Raney nickel catalyst using an initial hydrogen pressure of 3 atmospheres. When absorption of hydrogen ceased the catalyst was removed by filtration, the filtrate was concentrated under reduced pressure, and the product was purified by distillation under reduced pressure.

Hydrogenation of similar quantities of material was carried out in the same manner using 1.0 g. of platinum oxide (Adams) catalyst and 100 ml. of acetic acid as the solvent. The acetic acid was removed by addition of 20% sodium hydroxide and the product was collected by exhaustive extraction into ether, then purified by distillation under reduced pressure.

Procedure C.—Typical results for reduction with lithium aluminum hydride are described in the following account of an experiment with *dl-threo*-1-morpholino-2-nitro-1-phenylpropane. A solution of 15 g. (0.06 mole) of this amino nitro compound (m.p. 140–143°) in 175 ml. of anhydrous ether was added dropwise to a stirred solution of 6 g. (0.16 mole) of lithium aluminum hydride in 200 ml. of anhydrous ether. The rate of addition was regulated so that only a gentle refluxing of the ether was produced. The mixture was stirred for one hour after the addition was complete, then water was added cautiously to destroy the excess of lithium aluminum hydride. After addition of 250 ml. of a 20% sodium potassium tartrate solution the mixture was shaken, the ether layer was drawn off and the aqueous solution was extracted several times with ether. After the combined ether solutions had been dried over Drierite the solvent was removed by distillation and the residual oil was distilled under reduced pressure to yield 9.7 g. (75% yield) of a colorless oil, b.p. 150–159° (4 mm.).

From a 5-g. sample of this oil dissolved in petroleum ether (b.p. 30–60°) and kept under refrigeration impure *dl-threo*-1-morpholino-2-amino-1-phenylpropane separated in crystalline form, m.p. 70–79°. Following several recrystallizations from petroleum ether (30–60°) 2 g. of the pure *dl-threo*-diamine was obtained, m.p. 84–85°, as described below.

On the other hand, when the phenylthiourea was prepared from a 2-g. sample of the same oil the derivative obtained in pure form (0.2 g., 8% yield) after repeated recrystallization from 95% ethanol melted at 177–179° and proved to be the *dl-erythro* form described below.

Characterization of the Diamines Va, Vb and VI.—Individual diamines of the types V and VI are described below, together with the derivatives used in their characterization. Phenylthioureas were prepared by heating the diamines with phenyl isothiocyanate as in the procedure given by Shriner, Fuson and Curtin.[24] Sulfates were prepared by dissolving approximately 0.5 g. (or 0.0023 mole) of the diamine in 3 ml. of absolute ethanol and adding a solution of 0.23 g. (0.0023 mole) of concentrated sulfuric acid dissolved in 2 ml. of absolute ethanol. Isopropyl alcohol was then added dropwise until a cloudiness developed in the

(24) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 227.

solution, which was then cooled until crystallization occurred. The sulfates were recrystallized from absolute ethanol or absolute ethanol–isopropyl alcohol mixtures. *p*-**Toluenesulfonates** were prepared by adding solutions containing 0.85 g. (0.005 mole) of *p*-toluenesulfonic acid in 4 ml. of absolute ethanol to solutions prepared from approximately 0.44 g. (or 0.002 mole) of the diamine in 4 ml. of absolute ethanol. Crystallization was induced by cooling the mixture and the salts were then recrystallized from absolute ethanol.

dl-erythro-1-**Morpholino-2-amino-1-phenylpropane**.—The yield (procedure A) was 61.3% of a colorless oil, b.p. 150–153° (4 mm.). The phenylthiourea, *dl-erythro*-N-(1-methyl-2-morpholino-2-phenylethyl)-N′-phenylthiourea, was obtained in 80% yield, white needles from 95% ethanol, m.p. 177–179°.

Anal. Calcd. for $C_{20}H_{25}N_3OS$: C, 67.57; H, 7.09; N, 11.82. Found: C, 67.29; H, 7.23; N, 11.8.

The **sulfate**, apparently a monohydrate, was obtained in 55% yield as white needles, m.p. 184–185°. *Anal.* Calcd. for $C_{18}H_{20}N_2O \cdot H_2SO_4 \cdot H_2O$: C, 46.41; H, 6.59. Found: C, 46.25; H, 6.59.

The *p*-**toluenesulfonate**, apparently a monohydrate, was obtained in 61% yield as white platelets, instantaneous m.p. 153–154°. *Anal.* Calcd. for $C_{18}H_{20}N_2O \cdot 2C_7H_8O_3S \cdot H_2O$: C, 55.67; H, 6.53; N, 4.80. Found: C, 56.07; H, 6.50; N, 4.78.

dl-threo-1-**Morpholino-2-amino-1-phenylpropane**.—The yield was 66% by procedure A.; procedure B gave 62% with Raney nickel, 53% with platinum oxide. The colorless oil, b.p. 150–155° (4 mm.), solidified on cooling and was recrystallized from petroleum ether (b.p. 30–60°) to give fine white needles, m.p. 84–85°.

Anal. Calcd. for $C_{13}H_{20}N_2O$: C, 70.51; H, 9.22; N, 12.9. Found: C, 70.87; H, 9.15; N, 12.7.

The **phenylthiourea**, *dl-threo*-N-(1-methyl-2-morpholino-2-phenylethyl)-N′-phenylthiourea, was obtained in 85% yield as white needles from 95% ethanol, m.p. 184–185°. *Anal.* Calcd. for $C_{20}H_{25}N_3OS$: C, 67.57; H, 7.09; N, 11.82. Found: C, 67.46; H, 7.01; N, 11.7.

The melting point of a mixture of this thiourea derivative with that (m.p. 177–179°) obtained from the *erythro* form of the diamine was depressed to 170–175°.

A **benzoyl derivative**, *dl-threo*-1-morpholino-1-phenyl-2-benzamidopropane, which was obtained in 70% yield from the diamine by the Schotten–Baumann procedure, gave white needles, m.p. 166–167° from 95% ethanol.

Anal. Calcd. for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46. Found: C, 74.20; H, 7.48.

dl-erythro-1-**Piperidino-2-amino-1-phenylpropane**.—Procedure A gave a yield of 64% of colorless oil, b.p. 140–142° (4 mm.).[25]

The **phenylthiourea**, *dl-erythro*-N-(1-methyl-2-phenyl-2-piperidinoethyl)-N′-phenylthiourea, was obtained in 80% yield as white needles, m.p. 180–181° from 95% ethanol. *Anal.* Calcd. for $C_{21}H_{27}N_3S$: C, 71.34; H, 7.69; N, 11.89. Found: C, 71.77; H, 7.62; N, 11.8.

The **sulfate**, evidently a monohydrate, was obtained in 70% yield as fine white needles, m.p. 217–219° from absolute ethanol. *Anal.* Calcd. for $C_{14}H_{22}N_2 \cdot H_2SO_4 \cdot H_2O$: C, 50.27; H, 7.83; N, 8.38. Found: C, 50.30; H, 7.87; N, 7.95.

The *p*-**toluenesulfonate**, also a monohydrate, was obtained in 65% yield as fine white platelets, instantaneous m.p. 212–213°. *Anal.* Calcd. for $C_{14}H_{22}N_2 \cdot 2C_7H_8O_3S \cdot H_2O$: C, 57.93; H, 6.89. Found: C, 58.29; H, 7.00.

dl-threo-1-**Piperidino-2-amino-1-phenylpropane**.—Procedure A gave a 68.5% yield, procedure B (Raney nickel) a 51% yield of a colorless oil, b.p. 141–143° (4 mm.), which solidified. Recrystallization from *n*-hexane gave fine white needles, m.p. 51–52°.[26]

Anal. Calcd. for $C_{14}H_{22}N_2$: C, 77.01; H, 10.15; N, 12.83. Found: C, 76.75; H, 10.29; N, 12.8.

The **phenylthiourea**, *dl-threo*-N-(1-methyl-2-phenyl-2-piperidinoethyl)-N′-phenylthiourea, was obtained in 90% yield as white needles from 95% ethanol, m.p. 178–179°. *Anal.* Calcd. for $C_{21}H_{27}N_3S$: C, 71.34; H, 7.69; N, 11.89. Found: C, 71.09; H, 7.76; N, 11.7.

(25) Some samples of this compound have frozen when stored in a refrigerator.

(26) Melting points obtained for the free base were somewhat variable, and there are indications of a crystalline form melting at *ca.* 55°.

A small (1–2°) but reproducible melting point depression is observed when this derivative is mixed with the corresponding *erythro* derivative.

dl-erythro-**Pyrrolidino-2-amino-1-phenylpropane**.—Procedure A gave a 52% yield of a colorless oil, b.p. 105–107° (1 mm.).

The **phenylthiourea**, *dl-erythro*-N-(1-methyl-2-phenyl-2-pyrrolidinoethyl)-N′-phenylthiourea, was obtained in 70% yield as white prisms from 95% ethanol, m.p. 145–146°. *Anal.* Calcd. for $C_{20}H_{25}N_3S$: C, 70.75; H, 7.42; N, 12.38. Found: C, 70.89; H, 7.47; N, 12.2.

The *p*-**toluenesulfonate** was obtained in 60% yield as fine white needles, m.p. 220–222°. *Anal.* Calcd. for $C_{13}H_{20}N_2 \cdot 2C_7H_8O_3S$: C, 59.10; H, 6.61. Found: C, 59.04; H, 6.95.

Reduction of pyrrolidinium *dl*-1-pyrrolidino-2-*aci*-nitro-1-phenylpropane (III), essentially by procedure A, but using a solution prepared from approximately 6 *N* hydrochloric acid in double the usual volume to introduce the salt into the reduction mixture, gave a 30% yield of *dl-erythro*-1-pyrrolidino-2-amino-1-phenylpropane, and a quantitative recovery of pyrrolidine. The phenylthiourea prepared from the sample of *erythro*-diamine obtained in this way melted at 145–146° and was identical with that described above, as indicated by the mixed melting point test. There was no indication of the presence of the derivative of the *threo*-diamine described below.

dl-threo-1-**Pyrrolidino-2-amino-1-phenylpropane**.—Procedure A gave a 50% yield of a colorless oil, b.p. 130–134° (4 mm.).

The **phenylthiourea**, *dl-threo*-N-(1-methyl-2-phenyl-2-pyrrolidinoethyl)-N′-phenylthiourea, was obtained in 88% yield; white prisms from 95% ethanol, m.p. 145–146.5°. This m.p. is essentially the same as that of the *erythro* isomer, but the m.p. of a mixture of the diastereoisomers was markedly depressed.

Anal. Calcd. for $C_{20}H_{25}N_3S$: C, 70.75; H, 7.42; N, 12.38. Found: C, 70.79; H, 7.27; N, 12.5.

The *p*-**toluenesulfonate** was obtained in 66% yield, as white prisms from absolute ethanol, instantaneous m.p. 195–196°. *Anal.* Calcd. for $C_{13}H_{20}N_2 \cdot 2C_7H_8O_3S$: C, 59.10; H, 6.61. Found: C, 59.01; H, 6.66.

dl-threo-1-**Dimethylamino-2-amino-1-phenylpropane**.—Procedure A gave an 82% yield of a colorless oil, b.p. 80–83° (2 mm.).

The **phenylthiourea**, *dl-threo*-N-(1-methyl-2-dimethylamino-2-phenylethyl)-N′-phenylthiourea, was obtained in 90% yield; white platelets from 95% ethanol, m.p. 166–167°. *Anal.* Calcd. for $C_{18}H_{23}N_3S$: C, 68.97; N, 7.39; N, 13.40. Found: C, 68.89; H, 7.34; N, 13.2.

The **sulfate**, a monohydrate, was obtained in 77% yield; white leaflets from absolute ethanol, m.p. 190–192°. *Anal.* Calcd. for $C_{11}H_{18}N_2 \cdot H_2SO_4 \cdot H_2O$: C, 44.87; H, 7.55; N, 9.52. Found: C, 44.31; H, 7.19; N, 9.60.

The *p*-**toluenesulfonate**, a monohydrate, was obtained in 77% yield as fine white needles from absolute ethanol, instantaneous m.p. 155–156°. *Anal.* Calcd. for $C_{11}H_{18}N_2 \cdot 2C_7H_8O_3S \cdot H_2O$: C, 55.55; H, 6.84; N, 5.20. Found: C, 55.51; N, 6.82; N, 5.33.

dl-**Cyclohexylamino-2-amino-1-phenylpropane**.—Procedure A gave a 53% yield of a colorless oil, b.p. 125–130° (3 mm.).

The **phenylthiourea**, presumably *dl*-N-(1-methyl-2-cyclohexylamino-2-phenylethyl)-N′-phenylthiourea, was obtained in 90% yield; white needles from 95% ethanol, m.p. 173–175°. *Anal.* Calcd. for $C_{22}H_{29}N_3S$: C, 71.89; H, 7.95; N, 11.43. Found: C, 72.16; H, 7.84; N, 11.3.

The *p*-**toluenesulfonate** was obtained in 65% yield; fine white needles from absolute ethanol, m.p. 257–258°. *Anal.* Calcd. for $C_{15}H_{24}N_2 \cdot 2C_7H_8O_3S$: C, 60.38; H, 6.98. Found: C, 60.03; H, 7.17.

dl-**Benzylamino-2-amino-1-phenylpropane**.—Procedure A gave a 56% yield of a colorless oil, b.p. 162–165° (4 mm.).

The **phenylthiourea**, *dl*-N,N′-bis-(phenylthiocarbamyl)-1-benzylamino-2-amino-1-phenylpropane (VIIa), was obtained in 65% yield as white prisms from 95% ethanol, m.p. 165–166°.

Anal. Calcd. for $C_{30}H_{30}N_4S_2$: C, 70.55; H, 5.92; N, 10.97. Found: C, 70.21; H, 5.90; H, 10.9.

The *p*-**toluenesulfonate** was obtained in 68% yield; white prisms from absolute ethanol, m.p. 197–198°. The composition corresponds to that of a monohydrate.

Anal. Calcd. for $C_{16}H_{20}N_2\cdot2C_7H_8O_3S\cdot H_2O$: C, 59.80; H, 6.31. Found: C, 60.19; H, 6.58.

Deamination–Rearrangement Experiments with the Diamines V.—The nitrous acid reaction was carried out with both the *threo* and *erythro* forms of the morpholino and piperidino compounds and with the one (*threo*) form of the dimethylamino compound. Two different procedures were employed, one using hydrochloric acid, the other acetic acid.

In the hydrochloric acid procedure samples of the diamine (1.0–2.5 g.) were dissolved in 50–75 ml. of water by addition of slightly more than two moles of concentrated hydrochloric acid per mole of diamine. The solutions were cooled in an ice-bath and a solution of sodium nitrite (6–9 moles per mole of diamine) in water (5–10 ml.) was then added drop-wise. The solutions were stored in a refrigerator for two days, then made basic by addition of a 10% sodium hydroxide solution and extracted several times with ether. The ether solutions were extracted with 10% hydrochloric acid to remove unchanged starting material, then concentrated under reduced pressure to leave the deamination–rearrangement products as neutral residual oils. In most experiments some of the starting material was recovered by making the hydrochloric acid extracts basic and extracting with ether. The basic fraction obtained in this way was usually converted to a picrate for comparison with the picrate of the starting material.

In the experiments conducted in acetic acid solution 1.0–2.5-g. samples of the diamines were dissolved in 33–100 ml. of 50% aqueous acetic acid and treated at 2° with solutions of 1.0–5.0 g. of sodium nitrite dissolved in 5–10 ml. of water. Otherwise the procedure was essentially the same as in the experiments described above in which aqueous hydrochloric acid was used.

The neutral oils obtained from these experiments were converted into semicarbazones by use of a procedure given by Shriner, Fuson and Curtin.[27] In the experiments conducted with the *threo*- and *erythro*-morpholino compounds the infrared spectra of the crude semicarbazones were examined (in Nujol mulls) before the derivatives were recrystallized, then again after purification. Samples of the purified semicarbazones from the various experiments were identified with authentic samples of hydratropaldehyde semicarbazone, acetophenone semicarbazone or propiophenone semicarbazone by comparison of melting points, mixed melting points and, in the case of the experiments with the morpholino compounds, by comparison of infrared spectra. As shown by the data quoted below, the spectra of the three semicarbazones differed markedly in the 5.5–6.5 μ region of the infrared.

Results of experiments with individual diamines follow.

Reaction of *dl-erythro*-1-Morpholino-2-amino-1-phenylpropane.—When 1 g. of the diamine was treated with nitrous acid using the hydrochloric acid procedure a crude semicarbazone was obtained in three fractions; 0.23 g., m.p. 171–175°; 0.09 g., m.p. 165–170°; and 0.05 g., m.p. 155–170°. A Nujol mull prepared from a mixture of these three fractions displayed the infrared spectrum characteristic of propiophenone semicarbazone, with bands at 5.86(shoulder), 5.93, 6.02, 6.22(shoulder), 6.29 and 6.41 μ. Recrystallization of these crude products from 95% ethanol affected the spectrum merely in removing the shoulder at 5.86 μ and somewhat altering band intensities. A spectrum identical with that of the crude derivative was obtained from an authentic sample of propiophenone semicarbazone which had been recrystallized from 95% ethanol with seeding by a crystal taken from a recrystallized portion of the above derivative. However, another sample of propiophenone semicarbazone recrystallized from 95% ethanol without such seeding showed a slightly different spectrum, possibly either because of the presence of a second dimorphic form or because of a difference in crystal orientation in the Nujol mulls.[28] Bands observed in the 5.5–6.5 μ region were at 5.84, 5.96, 6.28(shoulder) and 6.39 μ. The bands at 5.84 and 5.97 μ in this sample may correspond to those at 5.93 and 6.03 μ in the other samples, and the 6.39 μ band was so

strong and broad as to suggest that it may have concealed the band at 6.29 μ (probably due to phenyl) observed in the other determinations.

Reaction of *dl-threo*-1-Morpholino-2-amino-1-phenylpropane.—When 1 g. of the diamine was treated with nitrous acid using the hydrochloric acid procedure a neutral oil weighing 0.414 g. was obtained. With semicarbazide, 0.3 g. of this oil yielded three crops of crystals: 0.24 g., m.p. 120–128°; 0.10 g., m.p. 128–130°; and 0.05 g., m.p. 135–150°. A Nujol mull prepared from a mixture of these three samples showed the following bands in the 5.5–6.5 μ region of the infrared: 5.75, 5.92, 6.07, 6.16, 6.26 and 6.32 μ (shoulder). Bands were found at 5.92, 6.06, 6.16 and 6.24 μ for hydratropaldehyde semicarbazone and at 5.75, 6.22 (shoulder) and 6.32 μ for acetophenone semicarbazone. Thus, the semicarbazone mixture from deamination–rearrangement had the spectrum of a mixture of hydratropaldehyde and acetophenone semicarbazones. (The 6.22 μ shoulder of acetophenone semicarbazone was obscured in the spectrum of the mixture by the strong 6.24 μ band of hydratropaldehyde semicarbazone.)

Reaction of *dl-erythro*-1-Piperidino-2-amino-1-phenylpropane.—When 1 g. of the diamine was treated with nitrous acid using the acetic acid procedure, 0.61 g. of neutral oil was obtained, and this yielded a crude semicarbazone, m.p. 160–165°. The m.p. was raised to 172–175° by one recrystallization from 95% ethanol. The yield of recrystallized derivative was 83%, assuming that the oil contained only propiophenone. No depression of the melting point was observed when this material was mixed with authentic propiophenone semicarbazone, m.p. 178–179°.

Reaction of *dl-threo*-1-Piperidino-2-amino-1-phenylpropane.—When 1 g. of the diamine was treated with nitrous acid using the acetic acid procedure the 0.5 g. of neutral oil obtained yielded a crude semicarbazone, m.p. 180–189°. Recrystallization from 95% ethanol raised the m.p. to 194–197°. The yield of recrystallized material would have been equivalent to 40% if the oil had consisted only of acetophenone. The melting point was not depressed by admixture of the sample with authentic acetophenone semicarbazone, m.p. 197–198°.

Reaction of *dl-threo*-1-Dimethylamino-2-amino-1-phenylpropane.—When 2.5 g. of the diamine was treated with nitrous acid by the hydrochloric acid procedure the 1.4 g. of neutral oil obtained yielded a crude semicarbazone, m.p. 120–140°. Following purification by recrystallization from 95% ethanol, the m.p. was raised to 149–150° and was not depressed by admixture of the sample with authentic hydratropaldehyde semicarbazone, m.p. 150–151°.

***dl-erythro*-1-Morpholino-2-nitro-1-phenylpropane from Sodium** *dl*-Morpholino-2-*aci*-nitro-1-phenylpropane.—A solution of the sodium salt of the *aci*-nitro form of 1-morpholino-2-nitro-1-phenylpropane was prepared by first dissolving 5 g. of *dl-threo*-1-morpholino-2-nitro-1-phenylpropane in 20 ml. of 20% hydrochloric acid, then adding the solution dropwise with stirring to 60 ml. of 10% sodium hydroxide. The resulting clear solution of the sodium salt was added dropwise with stirring to a solution prepared from 370 ml. of concentrated hydrochloric acid and 150 ml. of water. The acid solution, which remained clear, was allowed to stand for 24 hours to allow complete conversion of the *aci*-nitro form to the nitro form. A 120-ml. portion of the solution was carefully neutralized with sodium hydroxide solution. (A 20% solution was used until the end-point was approached, then a 5% solution.) The mixture was extracted with 50 ml. of ether, and the ether solution was dried over Drierite, then evaporated to leave 0.6 g. of a yellow oil, which failed to solidify. It was dissolved in 10 ml. of anhydrous ether and hydrogen chloride was passed into the solution. The oily hydrochloride which precipitated crystallized after it was dissolved in 3 ml. of absolute ethanol and the solution was diluted with ether. The 0.4 g. of white needles obtained, m.p. 111–112°, was dissolved in 3 ml. of water and 1% sodium hydroxide was added to the solution until no further precipitation occurred. The oily precipitate crystallized, and was filtered from the solution and washed with water. The white prisms so obtained melted at 83–84° and did not depress the m.p. of the *erythro* form, m.p. 84–85°, but a mixture with the *threo* form melted at 75–81°.

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(27) Ref. 24, p. 218. The procedure (B) for water-insoluble compounds was used.

(28) See discussion by F. A. Miller in H. Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, Vol. III, pp. 138–139.