column at 37° showed it to be a mixture of 1.2% of 1-methylcycloheptene and 98.8% of bicyclo[5.1.0]octane. A second experiment was done under identical conditions except it was run for 20 hr. Analysis showed the pyrolysate to contain 94.9% of bicyclo[5.1.0]octane, 2.3% of 1-methylcycloheptene and 2.8% of an unidentified material (not 1-ethylcyclohexene, cycloheptane or ethylidenecyclohexane).

Pyrolysis of Bicyclo[4.2.0]octane.—A 50-mg. sample of bicyclo[4.2.0]octane and a small amount of *n*-butyl hydrogen phthalate were heated in a sealed tube at 280° for 17 hr. Gas chromatograms of the product using the columns mentioned in the preceding experiment showed no 1-ethylcyclohexene. A blank was run at the same time by heating in another tube a sample of *n*-butyl hydrogen phthalate. The contents of the tube were analyzed by gas chromatography using the same columns, and a few small peaks appeared with retention times similar to the unknown material obtained from the above sealed tube pyrolysis of bicyclo[5.1.0]octane.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY 4, CALIF.]

Conformational Analysis in Symmetrically Substituted Cyclohexanones. The Alkyl Ketone Effects[1]

BY BRUCE RICKBORN

RECEIVED DECEMBER 8, 1961

The *cis–trans* equilibria and thermodynamic parameters of a series of 2,6-dialkylcyclohexanones have been evaluated and used as a measure of the 2-alkyl ketone effect. Though the effect is negligible for a methyl group, a smaller difference in conformational preference is found for ethyl, isopropyl and *t*-butyl substituents than that expected in the corresponding hydrocarbons. The magnitude of the 3-alkyl ketone effect for a methyl group was obtained from the menthone–isomenthone equilibrium. The conversion of a methylene group to carbonyl does not lower appreciably the energy of a 3-axial methyl substituent.

The conformational effects associated with an alkyl group substituted α or β in a cyclohexanone have been discussed by Klyne,[2] and by Robins and Walker.[3] Klyne, using earlier data of Johnston and Read,[4] calculated a value of 1.0 kcal./mole for the energy of interaction of an equatorial methyl group with an adjacent carbonyl group. Robins and Walker, following a suggestion made by Dreiding,[5] estimated that loss of one of the 1,3-methyl–hydrogen interactions would cause the energy of a 3-axial methyl group in a cyclohexanone to be half that found in the corresponding hydrocarbon.

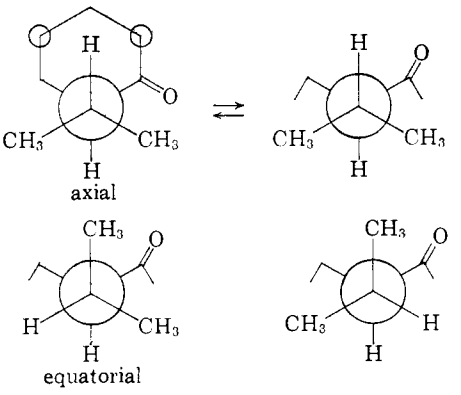
Allinger and Blatter[6] have recently obtained a direct measurement of the 2-alkyl ketone effect by examining the equilibria in a series of 2-alkyl-4-*t*-butylcyclohexanones. This work indicated that the effect was small, if present at all, for a methyl group,[7] but became appreciable for larger substituents.

In the present study the *cis–trans* isomerization of symmetrically substituted cyclohexanones has been used to obtain the magnitude of the 2-alkyl ketone effect. The equilibria and thermodynamic parameters for a series of 2,6-dialkylcyclohexanones have been evaluated. The results are shown in Table I.

The *cis* isomer in each case is essentially "frozen," as the alternate chair form has a 1,3-diaxial alkyl–alkyl interaction; even in the dimethyl compound, this conformation should make a negligible contribution.[8] The two chair conformations of the *trans* isomer are equivalent because of molecular symmetry.

Since the equilibrium in question involves the isomerization of a racemic mixture to a *meso* compound, the magnitude of the 2-alkyl ketone effect is obtained by correcting the observed free energy for the extraneous entropy of mixing of the DL-pair (−1.4 e.u.). This value should also be reflected in the experimentally determined entropy. The data in Table I indicate that this is the case for the methyl and ethyl substituted compounds; the experimental entropy terms for the isopropyl and *t*-butyl ketones, however, deviate considerably from that expected for a chair–chair interconversion.[9]

The slight positive ΔS associated with the *trans–cis* isomerization of 2,6-diisopropylcyclohexanone is presumably caused by the entropy of internal rotation of the isopropyl groups. Consideration of the staggered rotamers of equatorial and axial 2-isopropylcyclohexanone suggests that such a conversion would involve a positive entropy change



(1) Presented at the 141st Meeting of the American Chemical Society, Washington, D. C., March 26, 1962.

(2) W. Klyne, *Experientia*, **12**, 119 (1956).

(3) P. A. Robins and J. Walker, *Chemistry & Industry*, 772 (1955).

(4) R. G. Johnston and J. Read, *J. Chem. Soc.*, 1138 (1935).

(5) A. S. Dreiding, *Chemistry & Industry*, 1419 (1954).

(6) N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 944 (1961).

(7) A similar conclusion was drawn from the position of equilibrium for cholestan-6-one: N. L. Allinger, M. A. DaRooge, and R. B. Herman, *J. Org. Chem.*, **26**, 3626 (1961).

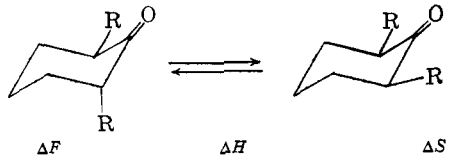
(8) N. L. Allinger and M. A. Miller, *J. Am. Chem. Soc.*, **83**, 2145 (1961).

(9) N. L. Allinger and L. A. Freiberg, *J. Am. Chem. Soc.*, **82**, 2393 (1960).

(10) The author is indebted to Professor N. L. Allinger for disclosure of this *A*-value for the isopropyl group prior to publication.

TABLE I

EQUILIBRIUM DATA FOR THE *trans–cis* INTERCONVERSION



R	*t*, °C.	% *cis*[a]	ΔF	ΔH	ΔS	ΔF (cor.)[c]	ΔA[d]
Me	25.0	91.59	−1.415	−1.95 ± 0.26	−1.8 ± 0.8	−1.82 ± 0.03	0
	90.7	85.76	−1.298				
Et	25.0	79.42	−0.800	−1.28 ± .16	−1.6 ± .5	−1.21 ± .03	0.9
	90.7	72.39	− .697				
i-Pr	25.0	56.22	− .148	+0.03 ± .07	+0.6 ± .2	−0.56 ± .01	1.5
	90.8	53.83	− .111				
t-Bu	25.0	86.63[b]	−1.107[b]	−2.02 ± .36	−3.1 ± 1.0	−1.52 ± .03	2.9
	50.0	83.26	−1.030				
	89.3	77.95	−0.909				

[a] These figures represent relative areas of vapor phase chromatography curves; the average deviation is about ±0.3% in each case. [b] Calculated from the data at higher temperatures (see Experimental). [c] ΔF (cor.) = ΔF (25°) − RT ln 2 (0.41 kcal.), to correct for optical isomerism of the *trans*-ketone. [d] ΔA is the difference between the A-values [S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955)] expected for the analogous hydrocarbons and the ΔF (cor.) values for the ketones; ΔF = −4.4 kcal./mole was used for 1,3-di-*t*-butylcyclohexane[9]; the A-value, 2.1 kcal./mole, was used for the isopropyl group.[10] ΔA is operationally equal to the 2-alkyl ketone effect as defined by Klyne, but, in the case of the *t*-butyl substituted ketone, is not a true measure of the energy involved in moving the group from an equatorial to an axial position (see text).

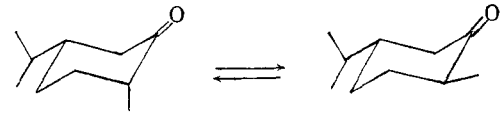
If the single rotamer (as shown) is the sole contributor to the axial conformation, and if the three equatorial rotamers contribute equally,[11] a maximum entropy of R ln 3 (2.2 e.u.) would be expected for this transformation. An experimentally observed entropy which differs from this value may simply be a reflection of the approximate character of these assumptions.[12]

The ΔF (cor.) terms in Table I show marked similarity to the corresponding values found by Allinger[6] in the 2-alkyl-4-*t*-butylcyclohexanone series. In both systems the change from methyl to ethyl to isopropyl causes a nearly constant decrease in ΔF (0.5 ± 0.1 kcal. per methyl group) for the axial-equatorial interconversion. When the α-substituent is *t*-butyl, the energy change increases, but, again, is essentially identical for both the 2,4- and 2,6-di-*t*-butylcyclohexanones.

The present data support the previous conclusion[6,7] that there is no measurable 2-alkyl ketone effect for the methyl group; the energy found for a 2-axial methyl group is 1.8 kcal., which is equivalent to its value in the corresponding hydrocarbon.[13]

In view of these results, a re-examination of Klyne's earlier arguments based on the reported[4] carvomenthone–isocarvomenthone equilibrium seemed in order. The value of this equilibrium constant was determined by polarimetric measurements, and suffers because the maximum rotations of carvomenthone and isocarvomenthone are not known with certainty.

Attempts to analyze directly a mixture of these ketones by vapor phase chromatography were unsuccessful. However, reduction of the equilibrium mixture with excess lithium aluminum hydride gave the four isomeric carvomenthols, which were separable by vapor phase chromatography. In this manner, the equilibrium mixture at 25° was found to contain 91 ± 1% carvomenthone. This corresponds to a ΔF of −1.4 kcal./mole, which is considerably larger than the value (−0.8 kcal./mole) used by Klyne in postulating the magnitude of of the 2-alkyl ketone effect for the methyl group. It is evident that in this system also, the conformational preference of the methyl group is nearly that expected for the corresponding hydrocarbon.



The 2,6-di-*t*-butylcyclohexanone data deserve separate consideration because of the magnitude of the entropy of the *trans–cis* interconversion. A residual entropy of −1.7 e.u. is obtained on correaction of the experimentally determined ΔS for the entropy of mixing of the DL-pair.[14] This value is in agreement with that found by Allinger for the isomerization of 2,4-di-*t*-butylcyclohexanone.[6] The conclusion drawn from the data for that system,

(11) The latter assumption has some justification in view of the small energy difference between *trans*- and *skew*-2,3-dimethylbutane: J. K. Brown and N. Sheppard, *J. Chem. Phys.*, **19**, 976 (1951).

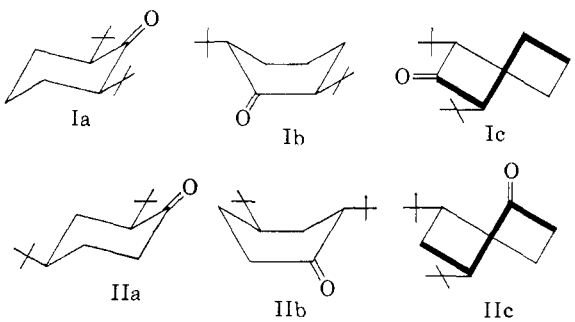
(12) ΔS = R ln 3 − R ln 2 = 0.8 e.u. is predicted on this basis for 2,6-diisopropylcyclohexanone. A rigorous treatment of the problem of entropy of internal rotation is given by Pitzer and Gwinn [K. S. Pitzer and W. D. Gwinn, *J. Chem. Phys.*, **10**, 428 (1942)]; see also S. Mizushima, "Structure of Molecules and Internal Rotation," Academic Press, Inc., New York, N. Y., 1954, p. 111.

(13) A recent measurement and discussion of the A-value for the methyl group is given by D. S. Noyce and L. J. Dolby, *J. Org. Chem.*, **26**, 3619 (1961).

(14) Arguments based on entropy values clearly are not precise, due to the unknown effects of internal rotation of ring substituents. It has recently been suggested that a non-chair conformation may be important in *trans*-2,5-di-*t*-butyl-1,4-cyclohexanedione [R. D. Stolow and C. B. Boyce, *J. Am. Chem. Soc.*, **83**, 3722 (1961)]. A low ΔS (0.2 e.u.) was observed for the *trans–cis* isomerization; as the *cis* compound exists in a non-chair conformation, it was stated that this low entropy value was not inconsistent with a similar conformation for the *trans*-diketone. It should be pointed out, however, that this system also involved the transformation of a *meso* compound to a DL-pair, and classically an entropy of R ln 2 would be expected for the interconversion of two like conformations. The equilibrium in this case (*ca.* 80% *cis*) speaks for the partial relief of the 2-*t*-butyl ketone effect in the non-chair conformation.

that the increased entropy was caused by the predominant contribution of nonchair conformation(s) in the *trans* isomer, appears to be also valid here.[14]

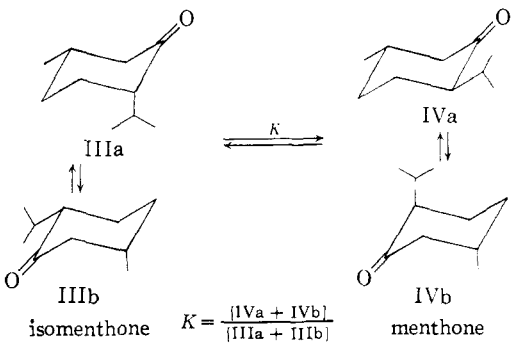
The identity of the energy difference between the *cis*- and *trans*-di-*t*-butyl isomers in both series is of interest, insofar as this result could not have been predicted *a priori*. In the *cis* isomer Ia the two bulky alkyl groups are nearly eclipsed[15] by the carbonyl oxygen. To the extent that the 2-alkyl ketone effect is caused by this eclipsing of an equatorial substituent (rather than a lowering of the energy of the axial conformation[6]), Ia should be less stable than its positional isomer IIa, which has only one such interaction. Conversely, a lower energy for the *trans* boat Ib, relative to IIb, is expected, since in Ib the *t*-butyl group in the gunwales position is no longer eclipsed by the carbonyl group, while in IIb (or in the *trans*-2,4-di-*t*-butylcyclohexanone boat conformation with a prow carbonyl) there is no relief of this interaction. Furthermore, the 4-*t*-butyl group in IIb is eclipsed by a hydrogen on the adjacent gunwales position. On the basis of such considerations, a smaller free energy change is predicted for the interconversion of Ia to Ib than for IIa to IIb.



In the twist[16] conformations Ic and IIc, however, the α-quasiequatorial substituents are still nearly eclipsed by the carbonyl oxygen; *i.e.*, the magnitude of this interaction is only slightly decreased by the *cis*-chair to *trans*-twist interconversion. The measured energies then apparently represent mainly the difference between chair and twist di-*t*-butylcyclohexanone and reflect only partially the energy associated with the 2-alkyl ketone effect for the *t*-butyl group.

Recently, Djerassi, *et al.*,[17] concluded from a rotatory dispersion study of 2-*t*-butyl-5-methylcyclohexanone that the twist form is the more important or even the exclusive conformation of the *cis* isomer. Furthermore, the equilibrium mixture (attained in refluxing methanol) was reported to contain 80% *trans* isomer (ΔF = 0.8 kcal./mole). This is entirely consistent with the di-*t*-butyl ketone data. Substitution of methyl for a *t*-butyl group will lower the energy of the twist form relative to the isomeric chair conformation by relieving somewhat the energy associated with the partially eclipsed alkyl group.[18]

The 3-Alkyl Ketone Effect.—The chair conformations of isomenthone and menthone are of interest as the equilibrium between these isomers can provide information regarding the 3-alkyl ketone effect. It has been suggested[19] that the sign and magnitude of the Cotton effect indicate that the axial isopropyl conformation IIIa is an important contributor to isomenthone. The low free energy change associated with moving an equatorial 2-isopropyl group to the axial position is in accord with this conclusion.[6,17] Further, the fact that this ΔF is the same for both 2-isopropyl-4-*t*-butylcyclohexanone and 2,6-diisopropylcyclohexanone strongly suggests that this value (0.57 ± 0.02 kcal.) can be applied to other systems.



In particular, it is possible to assign relative energies to the four chair conformations of menthone and isomenthone. Letting X equal the energy associated with an axial 5-methyl group, the conformations would have the following relative values: IIIa = 0.57, IIIb = X, IVa = 0, IVb = X + 0.57. Substitution into the observed equilibrium constant, K = 2.44 ± 0.04 (25°), allows the calculation of X. The energy of the 5-axial methyl group is > 1.8 kcal.[20] A value of 0.9 kcal. (as suggested by Robins and Walker)[3] gives a calculated equilibrium constant of 1.82. This corresponds to a mixture containing 64.5% menthone, considerably less than the experimentally determined amount (70.9 ± 0.3% menthone).

It appears that the substitution of a carbonyl group for a methylene group in cyclohexane does not appreciably lower the free energy of a 3-axial methyl substituent. Depending on the validity of the assumption that the conformational preference of the isopropyl group is unchanged, and on the choice of A value for the methyl group, the 3-alkyl ketone effect for methyl in this system is at most a few tenths of a kcal.

The equilibrium mentioned previously for 2-*t*-butyl-5-methylcyclohexanone supports this conclusion. Although the ΔF is nearly that which would be predicted if the chair conformation of the *cis* isomer (equatorial *t*-butyl, axial methyl) prevailed, and if the energy of the axial methyl group

(15) For a discussion of the geometry of chair cyclohexanone, see W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.*, **83**, 4013 (1961).

(16) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger and W. N. Hubbard, *ibid.*, **83**, 606 (1961).

(17) C. Djerassi, E. J. Warawa, J. M. Berdahl and E. J. Eisenbraun, *ibid.*, **83**, 3334 (1961).

(18) By similar argument, the twist conformation should be an important contributor (≥20%) in 2-*t*-butylcyclohexanone.[17]

(19) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, pp. 106, 187.

(20) Conformation IIIb thus contributes ≤ 15% to the over-all composition of isomenthone.

were 0.9 kcal., this isomer was found to contain an appreciable amount of the twist conformation.

Experimental

2,6-Dimethyl- and 2,6-Diisopropylcyclohexanone.—Hydrogenation (2000–2500 p.s.i., 170–230°, Raney nickel catalyst) of the symmetrical dialkylphenols gave isomeric mixtures of the corresponding cyclohexanols.[21,22] The mixed *cis*- and *trans*-ketones were obtained in high yield by chromic acid oxidation.[23]

2,6-Di-*t*-butylcyclohexanone.—Catalytic reduction of 2,6-di-*t*-butylphenol at 200°, 1700 p.s.i., 10% by weight Raney nickel, gave 2,6-di-*t*-butylcyclohexanone directly.[22] The mixture of ketones contained about 90% of the *cis* isomer, which was purified by recrystallization from aqueous methanol. The *trans* isomer, b.p. 144–145.5° (30 mm.), was obtained by fractional distillation of the residue.

2,6-Diethylcyclohexanone.—A mixture of *cis*- and *trans*-2,6-diethylcyclohexanone was prepared by pyrolysis of the barium salt of α,α'-diethylpimelic acid, following the procedure outlined by Newman, *et al.*[24]

Carvomenthone.—Hydrogenation (3 atm., 5% rhodium-on-alumina, rm. temp.) of carvone, $\alpha^{25}D$ 58.0° (1 dm., neat), gave a mixture of carvomenthone and isocarvomenthone, $\alpha^{25}D$ −25.1° (1 dm., neat).[4]

Geometry of the Isomeric Ketones.—The relative configurations of the 2,6-dialkylcyclohexanones were established by separation and collection of small amounts of each isomer by vapor phase chromatography followed by lithium aluminum hydride reduction. The *cis*-ketone in each case gave two isomeric alcohols, while only one was obtained from the *trans*-ketone, as determined by vapor phase chromatography.

Equilibration.—Equilibration of the ketones was in general effected by dilute sodium methoxide in methanol. Sealed test-tubes containing 2 ml. of the basic solution and about 0.1 g. of ketone were immersed in a constant temperature bath, removed at intervals, and the contents poured into a separatory funnel containing water and pentane. The pentane solution was evaporated and the residue was analyzed by vapor phase chromatography.

Potassium *t*-butoxide in *t*-butyl alcohol at 50° and 89° was used to equilibrate 2,6-di-*t*-butylcyclohexanone. These conditions were required because of the extreme stability of this system toward base; a 0.1 *M* solution of potassium *t*-butoxide in *t*-butyl alcohol at 25° caused isomerization at an inconveniently slow rate. A rough calculation[25] indicates that this compound is approximately 10^6 times less "acidic" than the dimethyl analog.

The diisopropyl ketone was examined in both solvents to assure no solvent dependency; no difference in the equilibrium constant was observed.

Analysis of Isomer Distribution.—A 10-foot 15% tricyanoethoxypropane-on-firebrick column was used at 100–140° for analysis of the ketones. Very clean separation of the *cis* and *trans* isomers was obtained in each case except for the carvomenthone–isocarvomenthone mixture. A planimeter was used to determine the areas of the chromatographic curves; at least forty of these curves were obtained for each equilibrium. The attainment of equilibrium was shown by the constancy of successive determinations. Each isomer was collected and recycled to show that no isomerization occurred during this process.

Lithium aluminum hydride reduction of mixtures of carvomenthone and isocarvomenthone having different rotations (and, hence, known relative isomer content)[4,26] gave mixtures of the four isomeric carvomenthols. These alcohols were separable by vapor phase chromatography, and, by using the different ketone mixtures, it was possible to relate each alcohol to the ketone from which it was derived. The equilibrium mixture (25°) of carvomenthone and isocarvomenthone gave 70.0% + 21% = 91 ± 1% carvomenthols and 7.6% + 1.4% = 9 ± 1% isocarvomenthols.

(21) R. B. Carlin, *J. Am. Chem. Soc.*, **67**, 928 (1945).

(22) T. H. Coffield, A. H. Filbey, G. G. Ecke and A. J. Kolka, *ibid.*, **79**, 5019 (1957).

(23) K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(24) M. S. Newman, I. Waltcher and H. F. Ginsberg, *J. Org. Chem.*, **17**, 962 (1952).

(25) D. J. Cram, B. Rickborn, C. A. Kingsbury and P. Haberfield, *J. Am. Chem. Soc.*, **83**, 3678 (1961).

(26) These mixtures were prepared by treatment with base at different temperatures; they differ only in the relative amounts of the 2-position isomers, being stereochemically equivalent at the 5-position.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, CAMBRIDGE 39, MASS.]

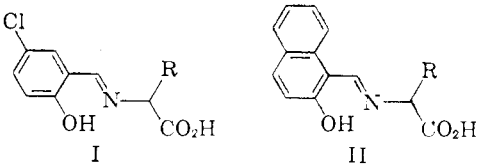
The N-(2-Hydroxyarylidene) Protecting Group in Peptide Synthesis

BY JOHN C. SHEEHAN AND VICTOR J. GRENDA[1]

RECEIVED FEBRUARY 5, 1962

5-Chlorosalicylaldehyde and 2-hydroxyl-1-naphthaldehyde have been used as reagents for the protection of amino functions during the synthesis of peptides. Thus, N-(5-chlorosalicylidene)-L-valine and N-(2-hydroxy-1-naphthal)-L-valine were coupled with ethyl glycinate and methyl L-phenylalaninate, employing N,N'-dicyclohexylcarbodiimide, to afford the corresponding N-(2-hydroxyarylidene) derivatives of L-valylglycine ethyl ester and L-valyl-L-phenylalanine methyl ester in good yield. Removal of the N-arylidene residues was accomplished under extraordinarily mild conditions of acid hydrolysis. No racemization of the peptide derivatives was observed.

Although benzaldehyde condenses readily with salts and esters of amino acids to afford Schiff bases,[2] analogous products with free amino acids have not been isolated,[2-4] with the exception of the ε-N-benzylidene derivative of the basic amino acid, L-lysine.[5,6] McIntire[7] investigated the reaction of a number of aromatic aldehydes with free amino acids at room temperature and reported the formation of crystalline Schiff bases (I and II) prepared in good yields from 5-chlorosalicylaldehyde and 2-hydroxy-1-naphthaldehyde, respectively.



The increased stability of these N-(2-hydroxyarylidene)-amino acids (as compared to the corresponding benzaldehyde analogs), which is ex-

(1) Bristol Laboratories Fellow 1958; U. S. Public Health Fellow 1959.

(2) M. Bergmann, H. Ensslin and L. Zervas, *Ber.*, **58**, 1034 (1925); O. Gerngross and E. Zuhlke, *ibid.*, **57**, 1482 (1924).

(3) H. Dakin, *J. Biol. Chem.*, **82**, 439 (1929).

(4) J. M. Gulland and T. H. Mead, *J. Chem. Soc.*, 210 (1935).

(5) M. Bergmann and L. Zervas, *Z. physiol. Chem.*, **182**, 282 (1926); **172**, 277 (1927).

(6) B. Witkop and T. W. Beiler, *J. Am. Chem. Soc.*, **76**, 5589 (1954).

(7) F. C. McIntire, *ibid.*, **69**, 1377 (1947).