Method A.—The suspension of phenylcopper in ether in the reaction flask prepared as described above, as it was, was refluxed with stirring under a nitrogen atmosphere at 35° for about 2 hr by substituting a Dimroth reflux condenser for the dropping funnel. Then, after substituting a Widmer fractionating column for the reflux condenser, 50 ml of xylene was added and most of ether was distilled off. Again, substituting the reflux condenser for the fractionating column, the reaction mixture was heated at 80° for 2 hr to complete the decomposition. The resulting products[15] in the solution were determined by gas chromatographic analysis as described below.

The suspension of phenylsilver in ether prepared as described above was refluxed at 35° for 4 hr in a similar manner to that of phenylcopper without addition of xylene. During the reaction a characteristic green color appeared transiently, gray metallic silver was produced in the flask, and a silver mirror appeared on the wall of the flask. The decomposition products in solution were analyzed by gas chromatography.

Method B.—The supernatant ether layer was decanted from the prepared phenylcopper (or phenylsilver) in ether. The remaining phenylcopper (or phenylsilver) precipitates were washed several times with cold ether having a temperature below −25°. Then, after adding 80 ml of cold ether, they were decomposed as described above.

In the experiments with *p*-benzoquinone, it was added to the phenylcopper suspension below −20° (or below −25° in the case of phenylsilver) immediately before the decompositions were carried out.

Competitive Decompositions of Copper Aryls and Silver Aryls in Suspension.—Phenylmagnesium bromide (0.040 mole) and *p*-tolylmagnesium bromide (0.040 mole) solutions in ether prepared separately were added dropwise to cuprous iodide (0.088 mole) in 120 ml of ether below −20° with vigorous stirring under a nitrogen atmosphere to obtain a mixture of phenylcopper and *p*-tolylcopper. After completing the reaction and confirming that unreacted Grignard reagents did not remain, the decomposition was carried out and the products were analyzed as described above (run 15). In a similar manner, a mixture of phenylsilver and *p*-tolylsilver was prepared, except that the reaction temperature was kept below −25°, and it was decomposed as was described in the case of phenylsilver (run 16).

In run 17, phenylcopper solid[16] (prepared from 0.030 mole of phenylmagnesium bromide and 0.036 mole of cuprous iodide in ether and washed with cold ether) and *p*-tolylcopper solid (prepared from 0.030 mole of *p*-tolylmagnesium bromide and 0.036 mole of cuprous iodide in ether and washed with cold ether) were mixed in 120 ml of ether below −20° in a vessel and were decomposed. In the above mixing, considerable amounts of both solids remained in the reaction flasks and were lost owing to their adherence to the flasks.

Competitive Decompositions of Silver Aryls in Pyridine Solution.—To the phenylsilver solid (prepared from 0.030 mole of phenylmagnesium bromide and 0.036 mole of silver bromide as indicated above) was added 40 ml of pyridine below −25°. The resulting mixture was stirred for about 2 hr and then filtered below −25° to obtain a clear, pale brown solution of phenylsilver in pyridine. In a similar manner, a solution of *p*-tolylsilver in pyridine was prepared. About 20 ml of each solution[17] were mixed together below −25° and added to 40 ml of cold pyridine and then decomposed at 50° for 2 hr. In these experiments, it is because of the low solubilities of the silver aryls in pyridine that the product yields were low (runs 19–21).

Quantitative Determination and Identification of the Products.—Quantitative determination of reaction products[18] was performed by gas chromatography (column, Silicone DC 550; carrier gas, H_2). As internal standards, toluene for benzene, benzene for toluene, *o*-nitrotoluene for biphenyl, and biphenyl for 4-methylbiphenyl and 4,4′-bitolyl were used.

Biphenyl, 4-methylbiphenyl, and 4,4′-bitolyl produced in competitive decompositions were identified by melting point measurements, measurements of mixture melting points with authentic samples, and infrared spectra for the samples which had been fraction-collected by gas chromatography.

(15) In method A, the amount of analyzed biphenyl was corrected by determining previously the biphenyl produced by Wurtz-type reaction during the preparation of phenylcopper.

(16) The compositions could not be determined exactly because the coordinated ether could not be removed completely even under a vacuum at a low temperature. The solid contained a small amount of magnesium salts (mole ratio of Cu to Mg *ca.* 20) as determined by analysis with 8-hydroxyquinoline.

(17) The concentrations of phenylsilver and *p*-tolylsilver were not determined because *r* is independent of them.

(18) It was found by preliminary experiments that the yields and compositions of the decomposition products were unchanged whether the reaction mixture was after-treated by water or not.

Conformational Analysis. XLVI. The Conformational Energies of the Simple Alkyl Groups[1-3]

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Received August 13, 1965

A series of 4-alkylcyclohexanecarboxylic acids has been prepared, and the *cis* ⇌ *trans* equilibria between the corresponding esters have been studied. The data allow the conformational free energies of the various groups to be calculated as follows (at 25° in ethanol solution): methyl, 1.8; ethyl, 1.8; isopropyl, 2.1; and carbethoxyl, 1.2 kcal/mole.

The conformational free energies ($\Delta G°$) of the simple alkyl groups are the basic quantities needed for the conformational analysis of cyclohexane ring systems. Prior to our studies, the conformational free energy of the methyl group was well established by thermodynamic methods,[4] while corresponding values for the ethyl[5] and isopropyl[5,6] were only very approximately known. Theory[7] indicates that the conformational free energies of the alkyl groups should increase in the order, methyl < ethyl < isopropyl < *t*-butyl, but the differences between the first three members of the

(1) Paper XLV: N. L. Allinger, M. A. Miller, L. W. Chow, R. A. Ford, and J. C. Graham, *J. Am. Chem. Soc.*, **87**, 3430 (1965).

(2) This investigation was supported by Public Health Service Research Grant A-5836 from the National Institute of Arthritis and Metabolic Diseases.

(3) Abstracted from the Ph.D. Dissertation submitted to the Graduate School of Wayne State University by L. A. Freiberg, March 1962. A preliminary communication outlining the present work was published earlier: N. L. Allinger, L. A. Freiberg, and S. Hu, *J. Am. Chem. Soc.*, **84**, 2836 (1962).

(4) (a) E. J. Prosen, W. H. Johnson, and F. D. Rossini, *J. Res. Natl. Bur. Std.*, **39**, 173 (1947); (b) J. E. Kilpatrick, H. G. Werner, C. W. Beckett, K. S. Pitzer and F. D. Rossini, *ibid.*, **39**, 523 (1947); (c) C. W. Beckett, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, **69**, 2488 (1947).

(5) (a) D. S. Noyce and L. J. Dolby, *J. Org. Chem.*, **26**, 3619 (1961); (b) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955); (c) A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, 4391 (1956).

(6) (a) N. Mori, and F. Suda, *Bull. Chem. Soc. Japan*, **36**, 227 (1963); (b) H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Koninkl. Ned. Akad. Wetenschap, Proc.*, **64B**, 161 (1961).

(7) (a) N. L. Allinger and S.-E. Hu, *J. Am. Chem. Soc.*, **84**, 370 (1962); (b) *J. Org. Chem.*, **27**, 3417 (1962).

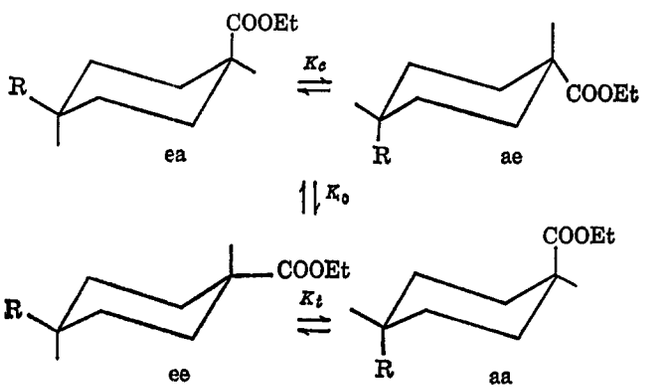
series should be small. High-temperature equilibration studies were carried out[7] which gave numerical values for the desired quantities that were consistent with expectations. The study reported herein was carried out concurrently with the high-temperature work, because the latter suffered from some uncertainty owing to the probable presence of boat forms in the equilibrium mixtures at the temperatures involved. Therefore, while ΔG° values for the high-temperature isomerizations could be accurately determined, their interpretation was less clear cut. The present study was beset with analytical difficulties and with the necessity of measuring sums and differences of two conformational free energies. The data here are therefore less accurate, but the interpretation is more straightforward. Thus, it was felt that agreement between the results obtained by the two methods would yield more convincing values for the desired quantities than would either investigation alone; hence, both were carried out.

Simultaneous with this work, another investigation was independently carried out by Lewin and Winstein[8] by a method similar in principle to that reported here, but the equilibrium involved was a conformational one and the analytical method used nmr. The good agreement between the results from all of these methods gives us confidence in the numerical values obtained. Recently similar measurements on different systems have been reported,[9] and these confirm the earlier values.

Discussion and Results

The equilibrium considered in the present work can be represented as shown in Chart I. In each case the

CHART I



observed equilibrium between the *cis* and *trans* isomers is K_0, and there are four conformations which require consideration, as shown. Boat forms can be neglected at the temperatures in question (below 150°), as can the forms aa and ae when R = *t*-Bu. The mathematical treatment of such a system has been worked out by Eliel and Ro.[10] The observed equilibrium constant is given by eq 1. The equilibrium constants

$$K_0 = ([ee] + [aa])/([ea] + [ae]) \quad (1)$$

K_R and K_{CO_2Et} for the reaction equatorial $\rightleftharpoons$ axial substituent are given by eq 2 and 3. To obtain K_R in

$$K_R = [ae]/[ee] = [aa]/[ea] \quad (2)$$

$$K_{CO_2Et} = [ea]/[ee] = [aa]/[ae] \quad (3)$$

terms of K_0 and K_{CO_2Et}, eq 1 may be transformed to $K_0[ea] - [ee] = [aa] - K_0[ae]$, and subsequently to

$$K_0K_{CO_2Et} - 1 = [aa]/[ee] - K_0K_R$$

Since

$$K_RK_{CO_2Et} = ([aa]/[ea])([ea]/[ee]) = [aa]/[ee] \quad (4)$$

it follows that

$$K_R = (K_0K_{CO_2Et} - 1)/(K_{CO_2Et} - K_0) \quad (5)$$

and

$$\Delta G^\circ_R = -RT \ln [(K_0K_{CO_2Et} - 1)/(K_{CO_2Et} - K_0)] \quad (6)$$

The values of ΔG°_R for methyl, ethyl, and isopropyl groups (calculated by eq 6 using the data reported in Table I) are assembled in Table II. For these calcu-

TABLE I

OBSERVED (UNCORRECTED) EQUILIBRIUM CONSTANTS FOR THE REACTION *cis*- $\rightleftharpoons$ *trans*-ETHYL 4-ALKYLCYCLOHEXANECARBOXYLATES

Alkyl		Temp, °K	K_0
t-Bu	*cis* (*c*)	415.7	4.762, 4.728, 4.628
	trans (*t*)	415.7	4.745, 4.780, 4.763
	c	376.7	5.393, 5.448, 5.360
	t	376.7	5.401, 5.460, 5.375
	c	352.4	6.093, 6.030, 5.906
	t	352.4	6.002, 5.980, 5.892
	c	329.4	6.510, 6.820, 6.836
	t	329.4	6.717, 6.747, 6.718
Me	*c*	416.0	3.394, 3.470, 3.395
	t	416.0	3.438, 3.357, 3.288
	c	375.2	4.052, 4.116, 4.125
	t	375.2	4.060, 3.960, 4.143
	c	352.6	4.386, 4.394, 4.374
	t	352.6	4.589, 4.493, 4.475
	c	329.7	5.022, 5.000, 4.803
	t	329.7	5.046, 5.158, 5.150
Et	*c*	416.2	3.324, 3.384, 3.500
	t	416.2	3.478, 3.427, 3.424
	c	374.7	4.022, 4.245, 4.287
	t	374.7	4.042, 4.218, 3.905
	c	354.0	4.306, 4.431, 4.374
	t	354.0	4.395, 4.375, 4.332
	c	329.9	4.902, 4.810, 4.862
	t	329.9	4.878, 5.034, 4.865

TABLE II

CONFORMATIONAL FREE ENERGIES AT 373°K IN ALCOHOL SOLUTION

Group	kcal/mole[a]
Carboethoxy	1.24
Methyl	1.98
Ethyl	1.97
Isopropyl	2.38

[a] ±0.10 kcal/mole.

lations, K_{CO_2Et} was calculated from $\Delta H^\circ_{373} = +1.105$ and $\Delta S^\circ_{373} = -0.372$ eu (obtained from the data where R = *t*-Bu) using the equation

$$K = e^{-\Delta H^\circ/RT}e^{\Delta S^\circ/R}$$

From these data the conformational free energies of the groups under investigation were deduced to be as in Table II. The data are not, unfortunately, of suf-

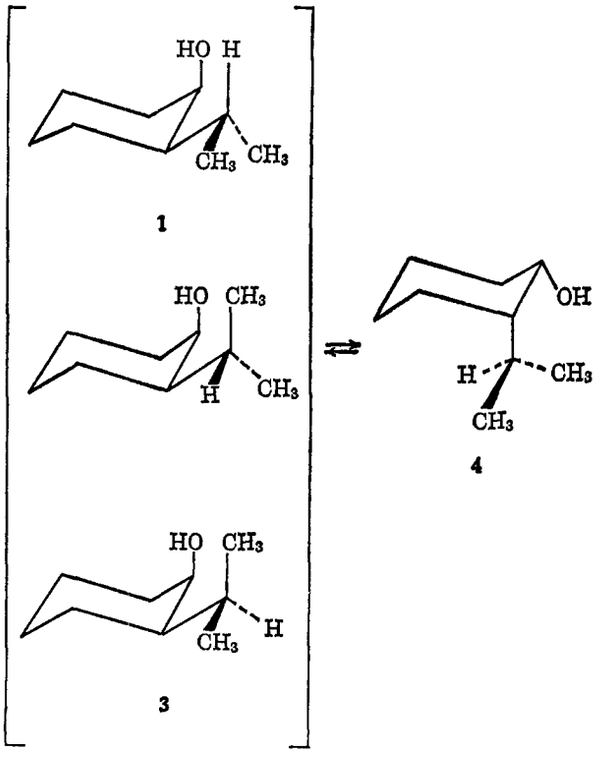
(8) A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962).
(9) B. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, **20**, 747 (1964).
(10) E. L. Eliel and R. S. Ro, *J. Am. Chem. Soc.*, **79**, 5992 (1957).

ficient accuracy to permit determination of $\Delta H°$ for the equilibria. Extrapolated to room temperature, the data yield conformational free energies of 1.8 kcal/mole for methyl and ethyl, and 2.1 kcal/mole for isopropyl, in good agreement with the values deduced[4-9] in other ways for the liquid phase.[11]

The earlier work of Winstein and Holness[5] on 4-isopropylcyclohexyl acid phthalate was correct in principle and should have led to correct values for $\Delta G°_R$ if all the assumptions made in the derivation of the Winstein–Holness equation are valid. It seems now that they are not all exactly valid,[12] and in their case (the *cis* isomer of the half-phthalate of 4-isopropylcyclohexanol), the conformational equilibrium is so one-sided that various factors such as small deformations of the rings by the attached substituents could lead to the observed result.

The large values obtained for the conformational energy of isopropyl by Noyce and Dolby and by Cole and Jefferies can also be interpreted now.[5] Examination of the conformational equilibria of *cis*-2-isopropylcyclohexanol, which contains the pertinent structural features, will reveal why. The equilibrium to be considered is represented in Chart II. There are *a priori*

CHART II



six possible chair conformations that this molecule may adopt (neglecting conformers differing by rotation about C–O bond). Of the three possible conformations of the axial isopropyl group, the two conformations with a methyl group over the cyclohexane ring are considered to be of very high energy and are neglected. Examination of the conformers **2** and **3** reveals a 1,3-diaxial-like hydroxy–methyl interaction estimated by Eliel and Haubenstock[13] to have an energy of 2.4 kcal/mole. The conformers **2** and **3** thus have high enough energies that they may be neglected in the present approximation, and the equilibrium really involves just **1** and **4**. The symmetry number of each of these conformations is 1, and, as each exists as a *dl* modification, the entropy difference then is expected to be negligible, and the difference in enthalpy will then represent the free-energy difference. The enthalpy of **4** with respect to zero interactions is three *gauche* interactions (each 0.9 kcal/mole), and one 1,3-diaxial hydroxy–methyl interaction (2.4 kcal/mole) or a sum of 5.1 kcal/mole. The enthalpy of **1** is 1.5 times an axial hydroxyl interaction (0.4 kcal/mole),[14] plus two *gauche* interactions, or 2.4 kcal/mole. The over-all enthalpy difference between **1** and **4** is therefore 2.7 kcal/mole. It is clear that this conformational free energy is about 1.0 kcal/mole higher than that estimated for *cis*-4-isopropylcyclohexanol (2.1 − 0.4 = 1.7 kcal/mole), where no vicinal interactions are possible, and, if the vicinal interactions of the hydroxyl and isopropyl are not taken into account for the type of system shown, the experimental value deduced for the conformational free energy of the isopropyl group will be too high. Thus, instead of 2.1 kcal/mole, Noyce and Dolby reported 3.2 kcal/mole, in approximate accord with the above calculations. The work of Cole and Jefferies[5] can be interpreted in a similar manner.[15]

Experimental Section

Ethyl *cis*-4-Ethylcyclohexanecarboxylate.—Ethyl *p*-ethylbenzoate, 74.6 g, was dissolved in 300 ml of acetic acid, 2.0 g of platinum oxide was added, and the compound was hydrogenated at 1–3-atm pressure. The hydrogen uptake was quantitative, and was completed in 18 hr. The solution was filtered, and the bulk of the acetic acid was removed by distillation. The residue was taken up in ether and washed with dilute sodium bicarbonate solution. Evaporation of the ether gave a quantitative yield of a mixture of ethyl *cis*- and *trans*-4-ethylcyclohexanecarboxylate. Analysis of the mixture by gas chromatography on a Tide column showed that it contained approximately 85% *cis* and 15% *trans*. This ester mixture was fractionally distilled through a 1-m packed column under nitrogen at atmospheric pressure. The initial fractions from this distillation were 95.5% *cis* and were combined and redistilled through a 1-m Podbielniak column and gave 0.5 g of the *cis* ester.

***cis*-4-Ethylcyclohexanecarboxylic Acid.**—The ester obtained above (which contained 15% of the *trans* isomer), 1.0 g, was saponified by refluxing for 30 hr with 30 ml of water containing 3.0 g of potassium hydroxide. The mixture was cooled and acidified with hydrochloric acid. The *cis* acid was isolated, but could not be induced to crystallize. It was distilled to yield 0.5 g of product.

***trans*-4-Ethylcyclohexanecarboxylic Acid.**—The crude *cis* ester, 18.4 g, was dissolved in a solution prepared from 0.23 g of sodium and 200 ml of absolute ethanol. The solution was heated under reflux for 72 hr, then 125 ml of alcohol was removed by distillation. A solution of 30 g of potassium hydroxide in 100 ml of water was then added, and the mixture was refluxed an additional 14 hr. The solution was cooled and acidified with concentrated hydrochloric acid, and the oil which separated was isolated by extraction with ether. The ether extracts were concentrated, diluted with petroleum ether (bp 60–90°) and cooled in Dry Ice–acetone. The precipitate was collected, and, after seven recrystallizations from 95% methanol at Dry Ice temperature, yielded 3.0 g (19%) of the *trans* acid.

(11) The values are somewhat higher in the gas phase, both theoretically and experimentally; see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division of John Wiley and Sons, Inc., New York, N. Y., 1965, p 174.

(12) See, for example, H. Kwart and T. Takeshita, *J. Am. Chem. Soc.*, **86**, 1161 (1964), and references therein.

(13) E. L. Eliel and H. Haubenstock, *J. Org. Chem.*, **26**, 3504 (1961).

(14) Reference 11, p 44.

(15) See also ref 11, p 148, and R. D. Stolow, *J. Am. Chem. Soc.*, **86**, 2170 (1964), for similar conclusion.

TABLE III

DATA ON 4-ALKYLCYCLOHEXANECARBOXYLIC ACIDS AND ETHYL ESTERS

Configuration	Alkyl	Compd	Mp or bp (mm), °C	$n^{25}D$	d^{25}_4	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
cis	Ethyl	Ester	227 (760)	1.4438	0.9358	$C_{11}H_{20}O_2$	71.69	10.94	71.83	10.84
trans	Ethyl	Ester	231 (760)	1.4413	0.9267		71.69	10.94	71.70	10.88
cis	Ethyl	Acid	127 (5)	1.4619		$C_9H_{16}O_2$	69.19	10.32	69.40	10.07
trans	Ethyl	Acid	49–49.8				69.19	10.32	68.90	10.18
cis	Isopropyl	Ester	243 (760)	1.4472	0.9345	$C_{12}H_{22}O_2$	72.68	11.18	72.56	11.43
trans	Isopropyl	Ester	245 (760)	1.4457	0.9263		72.68	11.18	72.62	11.08
cis	Isopropyl	Acid	41–42			$C_{10}H_{18}O_2$	70.55	10.66	70.53	10.69

Ethyl *trans*-4-Ethylcyclohexanecarboxylate.—A 2.8-g sample of the *trans* acid was esterified by dissolving in 25 ml of absolute ethanol containing 0.5 ml of concentrated sulfuric acid and heating the solution under reflux for 18 hr. The cooled solution was poured into water, and the product was extracted with ether. The ether extracts were washed with dilute sodium bicarbonate solution and water, and the solvent was evaporated. Distillation of the residue gave 2.44 g (74%) of the ester.

The corresponding series of 4-isopropylcyclohexanecarboxylic acids and esters were prepared similarly, and all the compounds were isomerically pure to the extent of at least 99%. The data are given in Table III.

The 4-methyl and 4-*t*-butyl compounds and the 4-*trans*-isopropylcyclohexanecarboxylic acid had properties in agreement with those reported in the literature.[16]

Equilibration Studies.—Temperatures were measured with calibrated thermometers or with a Leeds and Northrup potentiometer with an iron–constantan thermocouple, and are accurate to 1°. The absolute ethanol used in all equilibrations was used as obtained from the Commercial Solvents Corp.

For each temperature, equilibrium was attained starting from both the *cis* and *trans* esters. The time required to ensure that equilibrium was reached was determined by preliminary experiments. A typical run follows.

In 8 × 200 mm Pyrex combustion tubes were placed 0.25-ml samples of ester, one of which was 80% *cis*, the other 10% *cis*. To each tube was added 5.0 ml of alcohol containing 0.028 g of sodium. The tubes were flushed with nitrogen, sealed, and encased in metal cylinders, and were then placed in an electrically heated furnace thermostated at 366 ± 1°K. The samples were heated for 24 hr and were then quenched by removing the metal cylinders and plunging them into ice and water. The ester was isolated by extraction with 25 ml of ether. The ether was washed with ether-saturated sodium bicarbonate solution and dried over sodium sulfate. After removal of the ether by distillation through a 20-cm Vigreux column, the residue, a pale yellow liquid, was immediately analyzed at least three times by vapor phase chromatography on a Tide column. Analysis of *cis* and *trans* equilibration samples of a given compound were done consecutively.

The column used was a 7-mm Pyrex U, 190 cm in length, supported in a vertical heating jacket, and packed with 40–60 mesh Tide (Procter and Gamble). The column was operated at temperatures ranging from 170° for ethyl 4-*t*-butylcyclohexanecarboxylate to 110° for ethyl 4-methylcyclohexanecarboxylate.

The *cis* isomer was first eluted with each compound and had a retention time of 30–45 min. The isomers were all cleanly separated under the conditions described.

Equilibrium constants were calculated from the ratio of band areas which were calculated from peak-height, half-width measurements. The method of analysis was calibrated with samples of known composition, and it was found that the *trans* to *cis* ratio was consistently 0.97 of that observed. The observed values were correspondingly corrected.

(16) Subsequent to the completion of the present investigation, the 4-isopropylcyclohexanecarboxylic acids (having identical properties with those obtained herein) were reported by H. Van Bekkum, A. A. B. Kleis, D. Medema, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim.*, **81**, 833 (1962).

The Preparation and Structure of Hetacillin

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Received September 27, 1965

Hetacillin (2), a derivative of penicillanic acid with a unique structure, was prepared by the reaction of 6-[D-(−)-α-aminophenylacetamido]penicillanic acid (1) with acetone. The structure of hetacillin methyl ester hydrobromide was determined unequivocally by X-ray diffraction analysis.

We wish to report on hetacillin (2), a unique derivative of 6-aminopenicillanic acid in which the 6-amino group is part of an imidazolidinone ring. This compound can be prepared by the reaction of acetone with 6-[D-(−)-α-aminophenylacetamido]penicillanic acid (1), the amphoteric and clinically important semisynthetic penicillin known generically as ampicillin.

Hetacillin, which is the generic name for 6-(2,2-dimethyl-5-oxo-4-phenyl-1-imidazolidinyl)penicillanic acid, can be conveniently prepared from the reaction mixture of 6-aminopenicillanic acid with D-(−)-α-aminophenylacetyl chloride hydrochloride in aqueous acetone and is best isolated by crystallization from an aqueous medium at pH 2–3. It exhibits properties expected for an amino acid, forming both a crystalline potassium and a crystalline hydrochloride salt. It is soluble in neutral or strongly acidic aqueous solutions and sparingly soluble at pH 2–3. Its isoelectric point of 2.5 is somewhat lower than that of ampicillin (4.7), indicating reduced basicity of the side chain. Its stability toward acid is superior to that of ampicillin. Thus, for dilute aqueous solutions at pH 1 and 25°, the half-life of hetacillin was found to be 27–42 hr *vs.* 10–11 hr for ampicillin as measured by bioassay.

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