Juvala.[27] With the first of these the concentration of organic bromide was 0.016 M and of potassium iodide 0.0077 M; with the second the concentrations were 0.2 and 0.035 respectively. Both reactions were carried out in a thermostat at 24.90 ± 0.05°. The data were plotted according to the form of the equation for a bimolecular reaction

$$kt = \frac{2.303}{(M - 1)b} \log_{10} \frac{M - Z}{M(1 - Z)}$$

where M is the initial molecular proportion of organic bromide to inorganic iodide, b is the initial concentration of iodide, and Z is the fraction of iodide which has reacted in time t. The values of the rate constants were obtained from linear plots of this equation. They were not reproducible to better than 10%, but the uncertainty in the product made it seem pointless to attempt refinement of the method. Earlier runs with bromopropadiene employed material containing a few per cent. of 3-bromopropyne and with these it was necessary to calculate the constant starting from 15 to 20% reaction as zero time.

The reaction with chloropropadiene was carried out at 49.7 ± 0.1° and concentrations of 0.2 M for organic chloride and 0.04 M for potassium iodide. The value is less reliable because the reaction has proceeded only to the extent of 43% in five months.

3-Bromopropyne and Sodium Iodide.—From half-mole quantities of sodium iodide and 3-bromopropyne in anhydrous ethanol was obtained on standing for three days approximately the theoretical amount of sodium bromide. The filtrate was poured into ice-water and the organic layer washed once with water and dried over calcium chloride. The yield of C_3H_3I, b.p. 52–52.6° (100 mm.), $n^{20}D$ 1.6077 to 1.6112 (several fractions), was only 31% of theoretical. A small amount of forerun and 16% of high boiling material were obtained, but the remaining material was lost in the wash water. The C_3H_3I fraction had a broad boiling point at atmospheric pressure (109–115° with slight decomposition).

The experiment was repeated with one-fourth mole amounts using acetone as a solvent and maintaining a temperature below 20° at all times. The yield of C_3H_3I, b.p. 13.0–13.2° (10 mm.), was 9.6 g. (23%), $n^{20}D$ 1.5889, d^{20}_4 2.0430, MR obsd. 27.38, MR_D calcd. for HC≡CCH$_2$I 26.85, MR_D calcd. for H$_2$C=C=CHI 28.35 using 3.9 for the allene bond.[23]

Anal. Calcd. for C_3H_3I: C, 21.70; H, 1.82. Found: C, 22.36; H, 1.99.

When a sample of this compound was left at 40.0° the refractive index changed regularly, reaching a final value of 1.6210 after 10 days.

Bromopropadiene and sodium iodide (0.15 mole of each) were refluxed for 20 hours in 150 ml. of anhydrous acetone. The precipitate of sodium bromide was removed by filtration, two-thirds of the acetone was distilled through a column packed with helices and the residue was thrown into ice-water. The organic layer was washed with ice-water, dried over calcium chloride and fractionated at 195 mm. A small amount of bromopropadiene was recovered and 8.5 g. of material, b.p. 68.9–69.5°, $n^{20}D$ 1.5858–1.6032, was obtained (34% calculated as C_3H_3I). All fractions gave slight tests with 2,4-dinitrophenylhydrazine. The best fraction (b.p. 69.5°, $n^{20}D$ 1.6032, 4.3 g.) was washed thoroughly with sodium bisulfite solution and with water, dried over potassium carbonate and distilled to give material with $n^{20}D$ 1.6118. The remaining fractions were combined and treated similarly, giving a $n^{20}D$ 1.5989.

Infrared spectra were obtained with a Beckman IR 2½ spectrophotometer using rock salt cells, liquid samples and a cell thickness of about 0.03 mm.

LOS ANGELES, CALIFORNIA

(27) A. Juvala, *Ber.*, **63B**, 1995 (1930).

[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ARKANSAS]

The Relative Configurations of the 2- and 3-Hydroxycyclohexanecarboxylic Acids and the Related Methylcyclohexanols; the Stereochemistry of the Catalytic Hydrogenation of Substituted Cyclohexanones

BY SAMUEL SIEGEL

RECEIVED NOVEMBER 8, 1952

The configurations of the 2- and 3-hydroxycyclohexanecarboxylic acids have been related to the corresponding methylcyclohexanols by a series of chemical transformations which do not affect a center of assymmetry .Although the configurations of the 1,2-isomers are consistent with present designations, the configurations of the 3-methylcyclohexanols must be reversed. These results are consistent with current concepts of the stereochemistry of disubstituted cyclohexanes. An hypothesis is advanced to account for the predominance of the unstable isomer, and its configuration, in the catalytic hydrogenation of substituted cyclohexanones.

The assignment of configurations to isomeric disubstituted cyclohexanes has been unequivocal in the relatively few instances in which criteria of symmetry and/or the formation of cyclic compounds could be established.[1] Frequently the configurations are assigned by use of some empirical rule which is based upon differences in physical constants for geometrical isomers such as that of von Auwers.[2] The reassignment of the configurations of the 1,3-dimethylcyclohexanes by Beckett, Pitzer and Spitzer[3] as well as their able theoretical discussion of the energetics of disubstituted cyclohexanes excited our interest in the problem of obtaining chemical evidence for the configurational relationships among unsymmetrically disubstituted cyclohexanes. In particular, the configurations of 1,3-disubstituted cyclohexanes were suspect. In this paper chemical evidence for the relative configurations of the 2- and 3-hydroxycyclohexanecarboxylic acids and the corresponding 2- and 3-methylcyclohexanols is presented. The configuration of *trans*-4-hydroxycyclohexanecarboxylic acid has been related to *trans*-4-methylcyclohexanol by a method similar to the one used in this study.[4]

The configurations of the 2-hydroxycyclohexanecarboxylic acids are currently based upon their mode of formation and the physical properties of their derivatives,[5] and the 3-hydroxycyclohexanecarboxylic acids are assigned configurations upon

(1) H. Gilman, "Organic Chemistry," Second Edition, Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 478–482; Chapter written by C. S. Marvel.

(2) K. von Auwers, *Ann.*, **420**, 91 (1920).

(3) C. W. Beckett, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 2488 (1947).

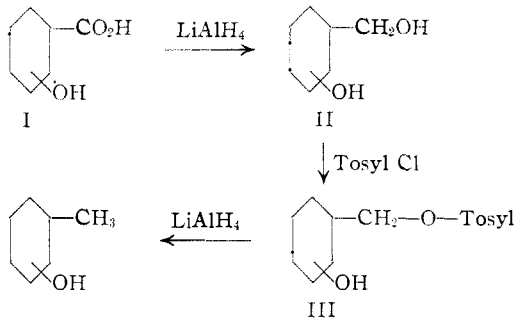
(4) L. N. Owens and P. A. Robins, *J. Chem. Soc.*, 326 (1949).

(5) J. Pascual, J. Sistare and A. Regas, *ibid.*, 1943 (1949).

the fact that only one of the isomers, the *cis*, can form a lactone and is reformed by hydrolysis of the lactone.[6]

The configurations assigned to the 2- and 3-methylcyclohexanols are based upon the method of synthesis and physical constants.[7-10] The more stable isomer is designated by the symbol α and is assumed to be *trans*, while the less stable isomer is called the β-form and assumed to have the *cis* configuration. These alcohols have not been related previously to compounds whose configurations are defined by more reliable criteria, as by the use of stereospecific reactions.[11]

The transformation of the hydroxy acids to the methylcyclohexanols proceeds as



The acid I is reduced with lithium aluminum hydride[12] to the glycol (II). The glycol (II) is selectively tosylated as described by Owens and Robins[4] to the monotosylate (III) which is in turn reduced with lithium aluminum hydride[13] to form the alcohol which is identified by conversion to suitable derivatives.

Experimental[14]

The 2-Methylcyclohexanol Derived from *cis*-2-Hydroxycyclohexanecarboxylic Acid.—*cis*-2-Hydroxycyclohexanecarboxylic acid (5.0 g., m.p. 80–81°, lit.[5] 80–81°), was reduced with $LiAlH_4$ according to the procedure recommended for substances slightly soluble in ether.[12] The glycol distilled at low pressure (0.1 mm.) and a bath temperature of 140–150° (yield 3.0 g.). The compound crystallized on standing, m.p. 49–50°.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.56; H, 10.84. Found: C, 64.89; H, 10.91.

The glycol (2.0 g.) was treated with a 10% excess of *p*-toluenesulfonyl chloride in dry pyridine which was added portionwise to the stirred mixture, cooled to −10°. The product was isolated by extraction with methylene chloride and freed of pyridine by washing with cold dilute hydrochloric acid. The extract was dried and concentrated. The crude product (2.1 g.) was reduced with $LiAlH_4$. The alcohol was isolated by extraction with ether. After evaporation of the solvent, 0.8 g. of the alcohol remained.

The alcohol was converted to the acid phthalate[11a] which crystallized readily when the reaction mixture was poured into cold water. The acid phthalate after one crystallization from dilute acetic acid melted at 103.5–105.5° (lit. 103–104°,[9] 104–105°[8]).

The 2-Methylcyclohexanol Derived from *trans*-2-Hydroxycyclohexanecarboxylic Acid.—*trans*-2-Hydroxycyclohexanecarboxylic acid, 5.0 g., m.p. 111° (lit.[5] 111°) was treated as above. The glycol (2.7 g., distilling at a bath temperature of 112–130° at 0.07 mm.) was not crystalline but the monotosylate (2.5 g. obtained from 2.2 g. of the glycol) melted at 75.5–76.5° after three recrystallizations from absolute ether.

Anal. Calcd. for $C_{14}H_{20}O_4S$: C, 59.11; H, 7.09; S, 11.27. Found: C, 59.25; H, 7.38; S, 11.31.

The alcohol, obtained by reduction of the tosylate, was converted to the acid phthalate[11a] which readily crystallized. After one recrystallization from dilute acetic acid it melted at 123.5–124.5° (lit.[8,9] 124–125°).

The 3-Methylcyclohexanol Derived from *cis*-3-Hydroxycyclohexanecarboxylic Acid.—*cis*-3-Hydroxycyclohexanecarboxylic acid, 15 g., m.p. 133.5–134.5° (lit.[6] 133–134°) was converted to the glycol as above, 7.5 g., b.p. 100–103° (0.3 mm.).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.56; H, 10.84. Found: C, 64.85; H, 10.91.

The conversion of the glycol to the monotosylate proceeded as before. A portion of the crude alcohol was converted to the *p*-nitrobenzoate (granular crystals) which melted at 53–55° after two recrystallizations, first from methanol and then from petroleum ether (30–60°). When mixed with the *p*-nitrobenzoate (m.p. 55–56°) of the alcohol (the α-form),[10,16] obtained from the $LiAlH_4$[15] reduction of 3-methylcyclohexanone, it gave no depression. There is some disagreement in the literature for the values of the melting points of the derivatives of the 3-methylcyclohexanols. Macbeth and Mills[10] give 48° for the melting point of the *p*-nitrobenzoate of the α-form, whereas Gough, Hunter and Kenyon[16] report 58°. They agree that the crystals separating from methanol are granular.

From 0.6 g. of the crude alcohol was obtained 0.6 g. of the acid phthalate which melted at 80–86°. After recrystallization from dilute acetic acid it melted at 90–92° (lit.[10] m.p. 94° for the α-form). It did not depress the melting point of an authentic sample of α-3-methylcyclohexanyl hydrogen phthalate.[10]

The 3-Methylcyclohexanol Derived from *trans*-3-Hydroxycyclohexanecarboxylic Acid.—*trans*-3-Hydroxycyclohexanecarboxylic acid, m.p. 121–122° (lit.[6] m.p. 122°), was converted as before to the glycol which distilled at 0.1 mm. and a bath temperature of 135–150°.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.56; H, 10.84. Found: C, 64.89; H, 10.91.

The monotosylate prepared as above was not isolated but was reduced to the alcohol. The alcohol was converted to the *p*-nitrobenzoate which crystallized from methanol as feathery needles, m.p. 60–61°. Macbeth and Mills[10] report a melting point of 63° for this derivative of the β-form while Gough, *et al.*,[16] gave 65°. Both agree that the crystalline form is flat, feathery needles. A mixture of this derivative and the *p*-nitrobenzoate obtained from the α-form, melted at 27–35°.

The acid phthalate, which was prepared from 0.6 g. of the crude alcohol, would not crystallize. It was converted to the piperazinium salt, which recrystallized from acetone to form glistening prisms, 0.6 g., m.p. 122–123°. The salt is identical to the piperazinium salt of authentic β-3-methylcyclohexanyl hydrogen phthalate.[10]

The discrepancies in the melting point of the derivatives of the 3-methylcyclohexanols reported in the literature and above are of concern but may be due to polymorphism which has already been demonstrated for the hydrogen phthalates and the phenylurethans.[10,11b] The direct comparison of derivatives of known history seems to offer the most reliable proof of identity.

Conclusions

It is clear that the relative configurations of the 2-methylcyclohexanols and the 2-hydroxycyclo-

(6) E. J. Boorman and R. P. Linstead, *ibid.*, 258 (1935).

(7) A. Skita and W. Faust, *Ber.*, **64B**, 2878 (1931).

(8) G. Vavon, A. Perlin and A. Horeau, *Bull. soc. chim.*, [4] **51**, 644 (1932).

(9) W. Hückel and K. Hagengurth, *Ber.*, **64B**, 2892 (1931).

(10) A. K. Macbeth and J. A. Mills, *J. Chem. Soc.*, 709 (1945).

(11) (a) See, however, R. B. Turner, THIS JOURNAL, **72**, 878 (1950). (b) NOTE ADDED IN PROOF.—After the acceptance of this paper, two independent studies establishing the configurations of the 3-methylcyclohexanols appeared: H. L. Goering and C. Serres, Jr., *ibid.*, **74**, 5908 (1952); D. S. Noyce and D. B. Denney, *ibid.*, **74**, 5912 (1952).

(12) R. F. Nystrom and W. G. Brown, *ibid.*, **69**, 1197 (1947).

(13) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949).

(14) Elementary analyses were performed by the Micro-Tech Laboratory, Skokie, Illinois.

(15) D. S. Noyce and D. B. Denney, THIS JOURNAL, **72**, 5743 (1950).

(16) G. A. C. Gough, H. Hunter and J. Kenyon, *J. Chem. Soc.*, 2062 (1926).

hexanecarboxylic acids are consistent with current assignments of configurations although the absolute configurations of neither pair of isomers can be said to be defined rigorously. However, it is evident that the configurations of the 3-methylcyclohexanols are inverted because the configurations of the 3-hydroxycyclohexanecarboxylic acids are firmly based upon reliable chemical evidence.[6]

The error in the previous assignment of configuration of the 3-methylcyclohexanols can be attributed to the classical notion that for a pair of geometrical isomers, the *trans* is the more stable one.[1,2,7] The statement that in acidic media the hydrogenation of a substituted cyclohexanone yields predominantly the *cis* isomer, also is misleading.[7,8]

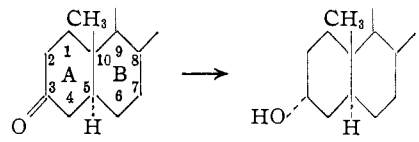
The application of the rules of von Auwers[2] and Skita[7] to the stereochemistry of disubstituted cyclohexanes can be evaluated in terms of the modern concepts of Hassel[17] and of Beckett, Pitzer and Spitzer.[3] Their studies suggest the hypothesis that for disubstituted cyclohexanes, any physical property which is in principle calculable as a statistical average of molecular properties, will be closely approximated at ordinary temperatures by the assumption that all the molecules exist in the same, *i.e.*, the most stable, conformation.[18] Because both substituents in *trans*-1,2-, *cis*-1,3-, and *trans*-1,4-disubstituted cyclohexanes can take up equatorial positions while the *cis*-1,2-, *trans*-1,3- and *cis*-1,4-disubstituted cyclohexanes are restricted to one polar and one equatorial position, the isomers in the first set will be more stable than the corresponding epimer.

Further, one may expect that properties such as density, refractive index, viscosity, dipole moments, etc., will differ between *cis* and *trans* isomers in a way which is predictable from the static model suggested above, and in particular, that the 1,3-isomers will differ in a sense opposite to that found in 1,2- and 1,4-isomers. Support for this conclusion may be obtained from the papers of Skita[19] and others.[20,21]

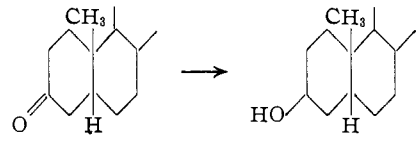
The stereochemistry of the catalytic hydrogenation of substituted cyclohexanones, which is frequently cited in support of a designation of configuration for cyclohexanols, may be reviewed profitably against the above background. Evidently, reduction of a cyclic ketone in acidic media leads to the formation of the less stable isomer.[7,22] Vavon[22] proposed that the production of the *cis*-alcohol in the reduction of 2-substituted cyclohexanones is due to steric hindrance between the entering hydrogen atom and the substituent. Linstead[23] agreed with the idea of a steric effect but assumed that it operates at the stage of adsorption of the molecule upon the surface of the catalyst. It is not clear how they would have transposed these ideas for ketones substituted at the more distant 3- and 4-positions where a classical sort of hindrance would be lessened.

Consider now that the stable conformation of a monosubstituted cyclohexanone is one in which the substituent is in an equatorial position and the carbonyl oxygen is included in the plane defined by the carbonyl carbon atom and the adjacent carbon atoms of the cycle. (The dipole moment of 2-phenylcyclohexanone[24] is consistent with this interpretation). If the molecule is adsorbed without change in conformation so that the carbonyl group is attached at two points, carbon and oxygen atoms, the least hindered arrangement will be one in which the cycle will tilt away from the surface of the catalyst. Addition of hydrogen from the direction of the catalyst will lead to the formation of a hydrogen–carbon bond (equatorial), *i.e.*, *trans* to a substituent in the 2-position and consequently a *cis* arrangement of substituent and hydroxyl group.[25] The parallel argument for the 3-substituted cyclohexanone predicts the formation of the *trans* substituted cyclohexanol while the 1,4-isomer should yield chiefly the *cis*-alcohol. From this point of view the stereospecificity of the reaction does not arise simply from steric hindrance between catalyst and substituent but rather to the steric interactions between substituent and the atoms of the cycle combined with the requirement of a precise orientation of the carbonyl group on the catalyst.

To our knowledge, 3-methylcyclohexanone is the only monosubstituted cyclohexanone with a substituent in the 3-position which has been reduced catalytically to a cyclohexanol whose configuration is adequately defined. Cholestanone (IV) and coprostanone (VI) are hydrogenated under acidic conditions to epicholestanol (V) and coprostanol (VII), respectively.[26] In both products, the HO-



IV V



VI VII

group and the arm of ring B which is attached at C-5 are *cis* to one another. These ketones thus follow the pattern predicted for 3-substituted cyclohexanones. This statement implies that the C-10 methyl group and the arm of ring B which is attached at C-10, interact about equally with the atoms of ring A in the manner described by Pitzer.[3] The premise is supported by the recent calculations

(17) O. Hassel, *Arch. Kjemi Bergvesen*, **3**, 32 (1943); O. Hassel and B. Ottar, *Arch. Math. Naturvidenskab*, **45**, No. 10, (1942).

(18) The chair conformation of the cycle and the equatorial positions for substituents are the preferred arrangements.

(19) A. Skita and R. Rossler, *Ber.*, **72B**, 265, 461 (1939).

(20) M. Mousseron and R. Granger, *Bull. soc. chim.*, **5**, 1618 (1939).

(21) R. Kuhn and A. Wassermann, *Helv. Chim. Acta*, **11**, 50 (1928).

(22) G. Vavon, *Bull. soc. chim.*, [4] **39**, 668 (1926).

(23) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine and R. R. Whetstone, THIS JOURNAL, **64**, 1985 (1942).

(24) E. L. Alpen and W. D. Kumler, *ibid.*, **72**, 5745 (1950).

(25) The addition of only *one* hydrogen atom, to the carbonyl carbon atom, is needed to fix the configuration of the product.

(26) L. Ruzicka, *Helv. Chim. Acta*, **19E**, 90 (1936).

of Turner[27] who showed that although the difference in energy between *cis*- and *trans*-decalin is 2.4 kcal. per mole, introducing an angular methyl group reduces the difference to 0.8 kcal., per mole.[28]

(27) R. B. Turner, THIS JOURNAL, **74**, 2118 (1952).

(28) See D. Barton, *Experientia*, **6**, 316 (1950), for a related discussion of the stereoisomerism found in sterols.

FAYETTEVILLE, ARKANSAS

[CONTRIBUTION FROM ABBOTT LABORATORIES]

The Preparation of Some N-Carbethoxyamino Acids

BY M. R. VERNSTEN AND M. B. MOORE

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Fifteen N-carbethoxyamino acids have been synthesized and examined for antiviral activity. Some have been tested as oncolytic agents as well, but none has proved to be of significant value.

In the course of screening compounds for antiviral activity, it was found that N-carbobenzoxy and N-carbethoxyglycylaminomalonic acid diethyl esters seemed to have a slight virus inhibiting effect.[1] It appeared possible that the malonic ester residue was unnecessary and that the N-substituted amino acids were functioning as antimetabolites against essential amino acids. This theory was tested by the synthesis of N-carbethoxy derivatives of some of the essential amino acids, and those from valine and phenylalanine showed some apparent activity.[1] This stimulated the synthesis of a whole series of such derivatives, but the inhibitory effects first observed were not later substantiated and none of the members showed antiviral activity of any significance.[1,2]

The carbethoxyamino acids are urethans and therefore were of interest in their effect on malignancies.[3] Those tested showed no inhibition of mouse sarcoma or leukemia.

Most of the amino acids used were the synthetic racemates and formed solid carbethoxy derivatives. It is of interest that when the *l*-form of the amino acid was used the product was frequently an oil.

Some of these N-carbethoxyamino acids have been prepared before by various methods.[4] The procedure employed here made use of the sodium salt of the amino acid rather than its ester and a second mole of alkali was furnished by sodium carbonate in the mixture from the beginning of the reaction. Equimolar quantities of α-amino acid, ethyl chloroformate, sodium hydroxide and sodium carbonate were used in the preparation of all the derivatives reported except that of lysine (in which case two moles of ethyl chloroformate and sodium carbonate were employed). It is noteworthy that the doubly substituted derivative of tyrosine as well as that of lysine was obtained, but that only monocarbethoxy derivatives were formed from tryptophan and serine. Apparently the hydrogens of the hydroxyl group of serine and the indole function of tryptophan are not sufficiently acidic to react with ethyl chloroformate under these reaction conditions.

The results obtained were fairly good with most of the α-amino acids used except *l*-arginine, *l*-histidine and *l*-cystine.[5] In these cases, the products isolated from the reaction of ethyl chloroformate with the amino acids were insufficiently pure to be reported.

Experimental[6]

N-Carbethoxyglycine.—Thirty-two grams (0.8 mole) of sodium hydroxide and 85 g. (0.8 mole) of sodium carbonate were dissolved in 500 ml. of water, stirred and cooled to 20° in an ice–salt-bath. To this solution was added 60 g. (0.8 mole) of glycine, and stirring and cooling were continued until the solution temperature dropped to 9.5°. Ethyl chloroformate, 87 g. (0.8 mole), was then added dropwise to the stirred solution at such a rate that the temperature did not rise above 10.5°. After stirring another hour in the cold and an additional two hours at room temperature, the reaction mixture was acidified by the careful addition of 100 ml. of concentrated hydrochloric acid solution, bringing the *p*H to about 4.

The resulting solution was concentrated to a sirup *in vacuo* on the steam-bath, and then to a sticky solid in an open evaporating dish. This residue was triturated portionwise with about a liter of ether; the ethereal solution dried by anhydrous magnesium sulfate, filtered and concentrated to about 100 ml. Addition of an equal volume of petroleum ether, b.p. 63–68°, caused the formation of an oil which slowly crystallized. The solid was separated by filtration, washed well with petroleum ether and dried; m.p. 73–74°,[7] yield 78 g. (66%).

By the same procedure as above (*i.e.*, equimolar quantities of amino acid, ethyl chloroformate, sodium hydroxide and sodium carbonate in water) at the temperature indicated, the following carbethoxy derivatives were prepared. The quantity of amino acid used, individual variations in working up the reaction mixture and purifying the product are given.

N-Carbethoxy-*dl*-alanine.—Reaction temperature 9 to 15°; 0.5 mole. The product was isolated by evaporation of the acidified reaction mixture and extraction of the residue with ether. The dried ethereal extract was evaporated to a sirup which slowly crystallized. The product was tritu-

(1) Private communication from C. J. Rickher, the late Dr. H. W. Cromwell and co-workers of Abbott Laboratories.

(2) Private communication from Dr. R. N. Bieter, University of Minnesota.

(3) E. Paterson, I. A. Thomas, A. Haddow and J. M. Watkinson, *Lancet*, [1], 677 (1946).

(4) (a) A. Hantzsch and W. V. Metcalf, *Ber.*, **29B**, 1680 (1896); (b) E. Fischer and E. Otto, *ibid.*, **36B**, 2108 (1903); (c) E. Fischer and W. Axhausen, *Ann.*, **340**, 123 (1905); (d) T. Curtius and W. Sieber, *Ber.*, **55B**, 1543 (1922); (e) L. Havestadt and R. Fricke, *ibid.*, **57B**, 2048 (1924); (f) E. Abderhalden and K. Kautzsch, *Z. physiol. Chem.*, **68**, 487 (1910).

(5) R. A. Gortner and W. F. Hoffman, *J. Biol. Chem.*, **72**, 433 (1927), report tetracarbethoxy-*l*-cystine as a deliquescent brown powder.

(6) All melting points are corrected.

(7) Reference 4a gives m.p. 67–69°; 4b, m.p. 75°.