C. Polymerization. Acid.—The vinyl compound (0.4 g.) was heated with one drop of 85% phosphoric acid at 80° for two hours. The product was a viscous oil insoluble in methanol but readily soluble in benzene.

Azodiisobutyronitrile.—The vinyl derivative (0.5 g.) was heated with 5 mg. of azodiisobutyronitrile at 80° for one hour. A further portion of 5 mg. of the catalyst was then added and the heating was continued for a total of two hours. The cooled product was a very viscous sirup. It was stirred with 2 cc. of methanol and filtered to give 0.25 g., m.p. 280–285°. The polymer was a tan powder insoluble in ether and methanol and soluble in chloroform and benzene. Clear brittle films were cast from benzene solution.

The yield of methanol-insoluble polymer was increased when larger amounts of catalyst and longer heating periods were employed.

Persulfate.—An emulsion consisting of 1 g. of XII, 1 ml. of water and 20 mg. of potassium persulfate was heated with stirring at 80° for six hours. The viscous polyvinyl derivative obtained was insoluble in methanol. When precipitated from benzene solution into methanol the product was an oil.

Cross-linking with Formaldehyde.—A 5-g. sample of solid polyvinyl derivative was heated six hours at 60° in 100 g. of hydrogen fluoride with 0.5 g. of paraformaldehyde. The reaction mixture was poured into water containing excess ascorbic acid. The resulting precipitate was filtered and washed with water until neutral. The cross-linked polymer thus obtained weighed 4.2 g. and was insoluble in boiling benzene.

Oxidation of the Polyvinyl Derivative.—A suspension of 1 g. of solid vinyl polymer in a solution of 2.5 g. of ceric sulfate in 50 ml. of water was stirred for two hours at room temperature. The dark blue solution obtained was filtered and the filtrate treated with excess ascorbic acid to give 1.0 g. of reduced polymer.

Copolymerization of the Vinyl Derivative. Methyl Methacrylate.—A solution of 2.0 g. of methyl methacrylate and 1.06 g. of XII (20 mole %) was heated at 80° for three hours with 30 mg. of azodiisobutyronitrile. The resulting polymer was dissolved in benzene (10 ml.) and added with stirring to 100 ml. of cold methanol. The copolymer weighed 2.0 g. and had m.p. 190–210°.

Anal. Calcd.: Fe, 9.12. Found: Fe, 10.3, 10.5.

The analysis indicates that 23.5 mole % of XII copolymerized. Films cast from benzene–chloroform solution were brittle.

Styrene.—A solution of 4 g. of the vinyl derivative (20 mole %) in 7.86 g. of styrene was heated at 80° two hours with 0.12 g. of azodiisobutyronitrile. The resulting viscous liquid was dissolved in benzene and the solution poured into methanol to obtain a yellow solid, 8.0 g., m.p. 158–165°.

Anal. Calcd.: Fe, 8.89. Found: Fe, 4.3, 4.2.

Films cast from benzene or chloroform were brittle.

Chloroprene.—A solution of 4.0 g. of Nancy Wood rosin, 5.0 g. of XII and 100 g. of chloroprene was emulsified under nitrogen with 100 ml. of water containing 1 g. of sodium hydroxide. The emulsion was transferred to a 500-ml. flask and stirred at 40° in a nitrogen atmosphere. One-half gram of potassium persulfate was added; polymerization began almost immediately. The temperature was maintained with the aid of an ice-bath at 39–41° until the reaction was complete (about one hour). The mixture was allowed to stir at room temperature for 20 minutes. The latex was coagulated by pouring into brine. The resulting orange-yellow, tough elastomer was washed on a washing mill and dried on a smooth mill at 100°. The mill dried product was dark brown, very tough and had an odor resembling, but fainter than, XII. The sample of mill-dried product showed the following analysis:

Anal. Calcd.: Fe, 1.21. Found: Fe, 1.15, 1.11.

Cyclopentadienyl-(ethylcyclopentadienyl)-iron (XIII).—Twenty grams of zinc was amalgamated by stirring ten minutes with 2 g. of mercuric chloride, 1 ml. of concentrated hydrochloric acid and 20 ml. of water. The aqueous phase was decanted and a mixture of 10 g. of the acetyl derivative I, 15 ml. of water and 20 ml. of concentrated hydrochloric acid was added. The reaction mixture was stirred under reflux for 18 hours. Five-ml. portions of acid were added at six hours and again at 12 hours after the start of the reaction. The product was separated with the aid of 100 ml. of ether. The ether solution was dried over magnesium sulfate and distilled through a short Vigreux section. Most of the material which distilled had b.p. 74–76° (0.2 mm.); the yield was 2.3 g. (25%).

Anal. Calcd. for $C_{12}H_{14}Fe$: C, 67.3; H, 6.59. Found: C, 67.3, 67.5; H, 6.67, 6.57.

DEEPWATER, NEW JERSEY

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Polysubstituted Cyclohexanes. The Synthesis of 9-Hydroxy-2-azabicyclo[3.3.1]nonane

BY FAUSTO RAMIREZ AND JOHN W. SARGENT[1]

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The preparation of *trans–cis-* and *cis–cis*-ethyl 3-amino-2-hydroxycyclohexaneacetate (XVa and XVb) from 2-carbethoxycyclohexanone, is reported. The synthesis of an isomer of 9-hydroxy-2-azabicyclo[3.3.1]nonane (XIX) is described. The stereochemistry of the amino alcohols XVa, XVb and XIX is discussed and a comparison is made between the behavior of isomeric vicinally trisubstituted cyclohexanes (type i) and simpler (1,2) and (1,3) disubstituted homologs (types ii, iii and iv).

Of significance in the chemistry of cyclohexane derivatives is the possibility of group interactions in polysubstituted systems, in particular as these interactions are affected by the relative configuration of the groups. Although conformational analysis has been applied mostly to polycyclic compounds,[2,3] it has proved to be of value also in an interpretation of the chemistry of simple and more flexible cyclohexanes.[4]

The present study is concerned with the behavior of stereoisomeric amino alcohol esters and acids of type i, in which the possibility exists for the formation of lactones (derivatives of 2-oxabicyclo[4.3.0]-nonane, v) or lactams (derivatives of 2-azabicyclo-

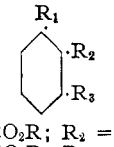
(1) From part of the Ph.D. Thesis of John W. Sargent.

(2) (a) H. D. Orloff, *Chem. Revs.*, **54**, 347 (1954); (b) O. Hassel, *Quart. Revs.*, **7**, 221 (1953).

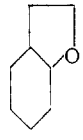
(3) (a) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); (b) W. S. Johnson, *Experientia*, **8**, 315 (1951).

(4) (a) D. Y. Curtin, *Record Chem. Progress*, **15**, 111 (1954); (b) J. F. J. Dippy, S. R. C. Hughes and J. W. Laxton, *J. Chem. Soc.*, 4102 (1954); (c) G. E. McCasland, THIS JOURNAL, **73**, 2295 (1951); (d) C. C. Price and G. Berti, *ibid.*, **76**, 1211 (1954); (e) D. Y. Curtin and S. Schmuckler, *ibid.*, **77**, 1105 (1955).

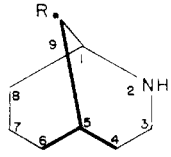
[3.3.1]nonanes, vi). The experiments were designed with the view of developing a stereospecific synthesis of 9-hydroxy-2-azabicyclo[3.3.1]nonane (9-hydroxymorphan, vi R = OH), a derivative of part of the ring system of morphine.[5] The synthesis of 2-azabicyclo[3.3.1]nonane (vi, R = H) was achieved for the first time in 1949 by Cronyn[6] and shortly thereafter by Ginsburg,[7] both investigators utilizing aromatic precursors and following similar routes.



i, $R_1 = CH_2CO_2R$; $R_2 = OH$; $R_3 = NH_2$
ii, $R_1 = CH_2CO_2R$; $R_2 = OH$; $R_3 = H$
iii, $R_1 = CH_2CO_2R$; $R_2 = H$; $R_3 = NH_2$
iv, $R_1 = H$; $R_2 = OH$; $R_3 = NH_2$



v



VI

The interactions of the pairs of functional groups which are found combined in structure i, have already been explored. Thus, Newman and VanderWerf[8] reported that *cis*-2-hydroxycyclohexaneacetic acid (*cis*-ii, R = H) formed a *cis*-lactone very readily; in fact, the *cis*-acid could not be isolated as it cyclized upon acidification of a solution of the sodium salt at 0°. On the other hand, *trans*-2-hydroxycyclohexaneacetic acid (*trans*-ii, R = H) did not cyclize in boiling water; the *trans*-acid formed a *trans*-lactone after several hours of reflux in dilute acid or upon heating at 200°.

Cronyn[6] showed that *cis*-3-aminocyclohexaneacetic acid (*cis*-iii, R = H) gave a lactam (derivative of vi, R = H) at 250°; the *trans*-acid failed to isomerize and/or cyclize under these conditions. *cis*-Ethyl 3-aminocyclohexaneacetate (*cis*-iii, R = C_2H_5) gave the lactam[6] at 200°; the *trans*-ester was recovered, mostly unchanged, under similar conditions. Ginsburg[7] achieved the cyclization of the *cis* acid iii (R = H) to the lactam at 200° (57% yield) and of the *cis* ester iii (R = C_2H_5) at 140–150° (88% yield).

The stereochemistry of the 2-aminocyclohexanols (iv) has received considerable attention[9] and the effect of configuration on group interaction, in particular in regard to nitrogen→oxygen acyl migrations, has been well established. The use of anhydrous hydrogen chloride in ethanol[9d] or dioxane[9c,10] has disclosed the greater tendency of the *cis*-2-benzamidocyclohexanol to undergo N → O acyl migration with retention of configuration, as compared to the *trans* isomer. Using thionyl chloride[9c] as reagent, the greater tendency of the *trans*-2-benzamidocyclohexanol to form a *cis*-oxazoline with inversion of configuration was brought out. The action of nitrous acid on the 2-aminocyclohexanols[11] (iv) has been found to give different results depending on the configuration of the amino alcohol. The *trans* isomer (*trans*-iv) gave a high yield of cyclopentylmethanal (ring contraction) while the *cis* isomer (*cis*-iv) gave a mixture of cyclohexanone (hydrogen migration) and cyclopentylmethanal, apparently richer in the latter.[12]

Results.—Chart I summarizes (a) the conversion of ethyl 1-carbethoxy-2-oxocyclohexaneacetate (I) into 3-carbethoxy-2-oxocyclohexaneacetic acid (IV) and (b) some transformations performed to substantiate the structure of the products.

Ethyl 1-carbethoxy-2-oxocyclohexaneacetate (I) was obtained by alkylation of 2-carbethoxycyclohexanone with ethyl bromoacetate and was converted directly into ethyl 3-carbethoxy-2-oxocyclohexaneacetate (II) in satisfactory yield.[13] Under certain conditions the product of the rearrangement of I was found to consist mainly of the non-ketonic triester III. 3-Carbethoxy-2-oxocyclohexaneacetic acid (IV), obtained by selective hydrolysis[14] of the β-keto ester-γ-keto ester II, could be isolated in crystalline keto and enol (V) forms. The nature of the tautomerism and the exclusion of the possible lactol form (ring-chain tautomerism) was based on spectral data in the ultraviolet and infrared, as described in the Experimental.

An enol lactone VII, readily obtained from the keto acid ester IV, was reduced stereospecifically to *cis*-3-carbethoxycyclohexaneacetic acid (VIII). The configuration of VIII was proven by a correlation through *cis*-3-carboxycyclohexaneacetic acid previously prepared.[15]

Chart II summarizes (a) the conversion of 3-carbethoxy-2-oxocyclohexaneacetic acid (IV) into one of the stereoisomeric forms of ethyl 3-amino-2-hydroxycyclohexaneacetate (XVa) and (b) the conversion of this amino alcohol ester into one of the stereoisomeric forms of 9-hydroxy-2-azabicyclo[3.3.1]nonane (XIX). The compounds included in Chart II are identified as belonging to the stereochemical series A. To this series, the *trans–cis* configuration[16] has been assigned on the basis of considerations summarized in the next section.

(5) (a) M. Gates, R. B. Woodward, W. F. Newhall and R. Kunzli, THIS JOURNAL, **72**, 1141 (1950); (b) R. Grewe and A. Mondon, *Ber.*, **81**, 279 (1948); (c) D. Ginsburg and R. Pappo, *J. Chem. Soc.*, 15 (1953).

(6) (a) M. W. Cronyn, *J. Org. Chem.*, **14**, 1013 (1949); (b) see also M. W. Cronyn and G. H. Riesser, THIS JOURNAL, **75**, 1664 (1953).

(7) D. Ginsburg, *J. Org. Chem.*, **15**, 1003 (1950).

(8) M. S. Newman and C. A. VanderWerf, THIS JOURNAL, **67**, 233 (1945).

(9) (a) G. E. McCasland and D. A. Smith, *ibid.*, **72**, 2190 (1950); (b) G. E. McCasland, R. K. Clark, Jr., and H. F. Carter, *ibid.*, **71**, 637 (1949); (c) W. S. Johnson and E. N. Schubert, *ibid.*, **72**, 2187 (1950); (d) G. Fodor and J. Kiss, *ibid.*, **72**, 3495 (1950).

(10) E. E. van Tamelen, *ibid.*, **73**, 5773 (1951).

(11) G. E. McCasland, *ibid.*, **73**, 2293 (1951).

(12) For the mechanism of nitrous acid deamination of amino alcohols and a more exact interpretation of the results of ref. 11 based on energies of the possible transition states see ref. 4a, e and bibliography therein; see also D. Y. Curtin and M. C. Crew, THIS JOURNAL, **77**, 354 (1955).

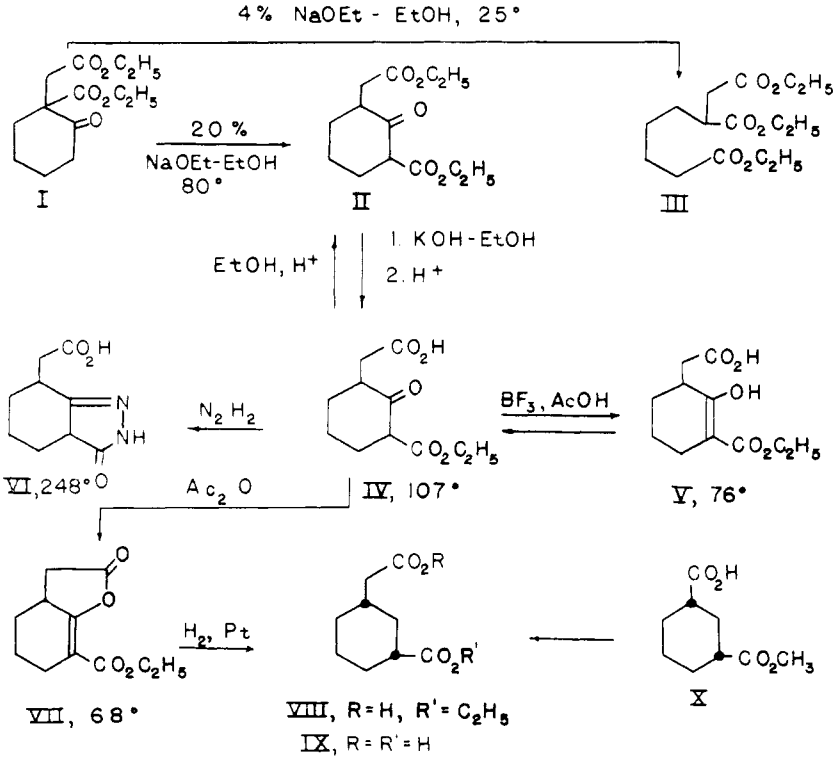
(13) For similar utilization of Claisen-type equilibria in alicyclic systems see H. T. Openshaw and R. Robinson, *J. Chem. Soc.*, 941 (1937).

(14) R. Richter, *Helv. Chim. Acta*, **32**, 2318 (1949).

(15) F. Ramirez and J. W. Sargent, THIS JOURNAL, **74**, 5785 (1952).

(16) The term *trans–cis* refers to the configurations at C_2 and C_3, respectively, with reference to the side chain at C_1. The acetic acid side chain at C_1 is written below the plane of the paper. A heavy dot represents a hydrogen atom projecting above the plane of the paper. The products shown were isolated in pure form; the formation of other isomers in smaller amounts is not excluded.

CHART I

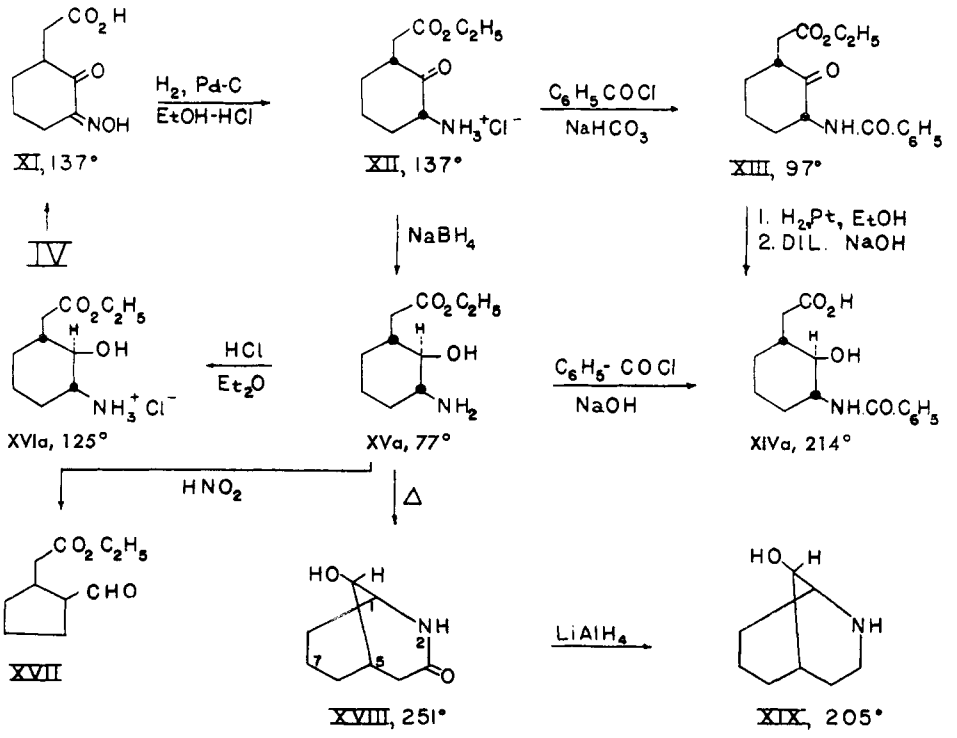


The replacement of the carbethoxy group of 3-carbethoxy-2-oxocyclohexaneacetic acid (IV) by the oximino group to yield 3-oximino-2-oxocyclohexaneacetic acid (XI) proceeded satisfactorily.[17] Catalytic hydrogenation of the oximino keto acid XI, following Hartung's procedure,[18] gave *cis*-ethyl 3-amino-2-oxocyclohexaneacetate hydrochloride (XII). Reduction of the hydrochloride XII with sodium borohydride yielded one isolable crystalline isomer formulated as *trans–cis*-ethyl 3-amino-2-hydroxycyclohexaneacetate (XVa). Benzoylation of XVa in the presence of alkali gave *trans–cis*-3-benzamido-2-hydroxycyclohexaneacetic acid (XIVa), identical with the substance obtained by catalytic hydrogenation of *cis*-ethyl 3-benzamido-2-oxocyclohexaneacetate (XIII) in *neutral* medium, followed by mild alkaline hydrolysis. On heating, the amino alcohol ester XVa gave a high melting substance whose analysis, molecular weight and infrared spectrum were in agreement with those of 9-hydroxy-3-oxo-2-azabicyclo[3.3.1]nonane (XVIII). Reduction of the hydroxylactam XVIII yielded 9-hydroxy-2-azabicyclo[3.3.1]-nonane (XIX). The nitrous acid deamination of *trans–cis*-ethyl 3-amino-2-hydroxycyclohexaneacetate (XVa) afforded, as the only carbonyl product, ethyl 2-formylcyclopentaneacetate (XVII).

Chart III summarizes the preparation of another of the possible stereoisomers of ethyl 3-amino-2-hydroxycyclohexaneacetate (XVb). The compounds included in Chart III are identified as belonging to series B and differ from those of series A in the configuration of the hydroxyl-bearing carbon. To series B the *cis–cis* config-

CHART II

TRANS-CIS SERIES

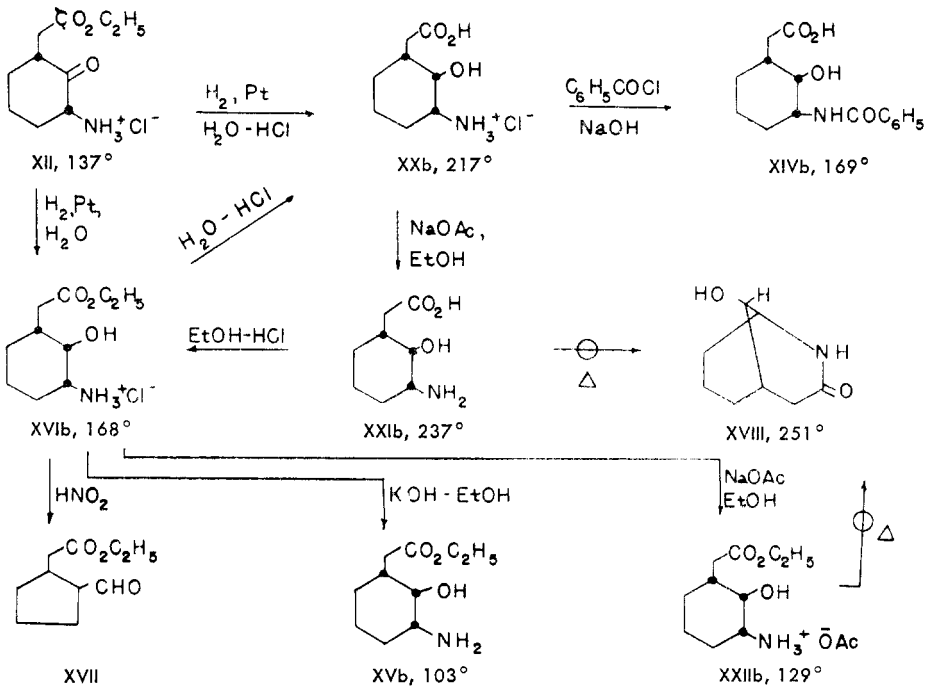


(17) *Inter alia* T. A. Geissman and N. J. Schlatter, *J. Org. Chem.*, **11**, 771 (1946).

(18) W. H. Hartung and Y. Chang, THIS JOURNAL, **75**, 89 (1953).

CHART III

CIS-CIS SERIES



uration[16] has been assigned (*vide infra*).

It should be noted that catalytic hydrogenation of *cis*-ethyl 3-amino-2-oxocyclohexaneacetate hydrochloride (XII) in strongly acidic (XII → XXb) or in weakly acidic (XII → XVIb) media gave alcohols of the same configuration. The stereochemical correspondence of the various compounds in series B is also summarized in Chart III. *cis–cis*-3-Amino-2-hydroxycyclohexaneacetic acid hydrochloride (XXb) and *cis–cis*-ethyl 3-amino-2-hydroxycyclohexaneacetate hydrochloride (XVIb) could be regenerated from the free amine XXIb or the amine acetate XXIIb, respectively, by treatment with hydrochloric acid.

In contrast to the *trans–cis*-amino alcohol ester XVa, the *cis–cis*-isomer XVb failed to yield a hydroxy lactam on heating; in the latter case only amorphous and intractable solids were formed. On the other hand, pyrolysis of either *cis–cis*-3-amino-2-hydroxycyclohexaneacetic acid (XXIb) or the acetate salt XXIIb led to a product shown to be identical with the previously obtained hydroxy lactam XVIII. The details of the epimerization implied in the formation of lactam XVIII from compounds of the *cis–cis* series are not known.[19] In this connection it should be noted that a sample of lactam XVIII (m.p. 251–253°) when kept slightly above its melting point for several minutes remelted at approximately 203°–; Table I summarizes the behavior of the various amino alcohols upon heating.

(19) The alkoxide-catalyzed stereochemical equilibrium of carbinols is initiated by carbonyl compounds (W. von E. Doering and T. C. Aschner, THIS JOURNAL, **75**, 393 (1953)). The equilibrium is known to be established, although slowly, at elevated temperatures in the "absence" of alkoxides (W. Ponndorf, *Z. angew. Chem.*, **39**, 138 (1926); R. W. Young, Dissertation, Columbia University, 1951, p. 12).

Stereochemical Considerations.—The configurations assigned to compounds of series A and B (Charts II and III) are believed to represent a self-consistent interpretation of the results of (a) cyclization experiments, (b) catalytic hydrogenation of ketones in neutral and in acid media[20,21] and (c) sodium borohydride reduction of the ketones.[20] The configurational assignments are strengthened by observations discussed in the next section of this paper.

The establishment of a *cis* configuration of the amino group at C_3 and the acetic acid side chain at C_1 during hydrogenation of 3-oximino-2-oxocyclohexaneacetic acid (XI → XII, Chart II) was anticipated, since the presence of an α-keto group and the acidic conditions of the medium should ensure formation of the more stable isomer XII[22] (see Fig. 1, A-hydrochloride).

TABLE I

BEHAVIOR OF AMINO ALCOHOLS ON HEATING

Compound	Crude product[a] M.p., °C.	Yield, %	Pure product[b] M.p., °C.	Yield, %
trans–cis-Amino alcohol ester XVa	206–	94	251–253	57
cis–cis-Amino alcohol ester XVb	Amorphous solids			
cis–cis-Amino alcohol acid XXIb	210–	79	250–252	60
cis–cis-Amino alcohol ester acetate XXIIb	205–	77	251–253	65

[a] Sublimed but unrecrystallized. [b] Sublimed and recrystallized.

(20) The rules given (ref. 3a; *cf.* ref. 2a, page 380) for the catalytic reduction of cyclohexanones in *neutral* medium (equatorial alcohol predominant) and for the sodium borohydride and lithium aluminum hydride reductions (equatorial alcohol predominant) are not without ambiguity, since they involve an indeterminate degree of hindrance of the ketone. Catalytic hydrogenation of both hindered and unhindered ketones in strongly *acidic* media is said to yield axial alcohols. In *flexible* cyclohexanones, the configuration of the resulting molecule would depend on the conformation chosen for the substrate, as well as on the course and mode of addition of hydrogen.

(21) For a recent interpretation of the course of catalytic hydrogenation of cyclohexanones in neutral and in acid media see J. H. Brewster, THIS JOURNAL, **76**, 6361 (1954).

(22) In 1,3-disubstituted cyclohexanes, the *cis*-1e,3e conformation is considerably more stable than the *cis*-1a,3a conformation (ref. 2a, pp. 355, 357). Among disubstituted cyclohexanes the (*trans*-1,2), (*cis*-1,3) and (*trans*-1,4) forms (ee ⇄ aa) are regarded, in general, as the more stable of the corresponding isomeric pairs (ref. 2a, p. 357). In the modified Auwers–Skita rules (ref. 2a, p. 358; N. Allinger, *Experientia*, **10**, 1 (1954)) these forms are expected to have the higher melting point, and the lower solubility, refractive index, density and

That this was the case was shown by the cyclization of the product of further reduction, namely, the amino alcohol ester XVa, to the bicyclic lactam XVIII under conditions known[6,7] to preserve the C_1–C_3 configuration in similar systems (iii).

Catalytic hydrogenation of the N-benzoyl keto ester XIII (Chart II) in *neutral* medium should yield preponderantly an equatorial alcohol[20,21,23] (Fig. 1, B, as N-benzoyl), hence, it should give rise to the *trans–cis* configuration XIVa. The configuration of XIVa is consistent with the results of the sodium borohydride reduction of the amino keto ester hydrochloride XII, which should yield predominantly an equatorial hydroxyl[20,21] as in XVa. The alcohols produced in both types of reductions were shown to be stereochemically related (XVa → XIVa).

The alcohol formed in the catalytic hydrogenation of the amino keto ester hydrochloride XII (Chart III) in *strongly acidic* medium should be predominantly of the axial conformation[20,21,23] (Fig. 1, C, as hydrochloride), hence it should have the *cis–cis*-configuration XXb (Chart III). Catalytic hydrogenation of an aqueous solution of the hydrochloride XII (no added mineral acid) was found to yield alcohol of the same stereochemical series, hence *cis–cis*-XVIb with axial hydroxyl,[20,21,23] as shown by the various correlations of Chart III.[24]

The evidence for the configuration of the hydroxy lactam XVIII and the amino alcohol XIX is largely negative in character. Thus, no oxazolidine derivative[25] could be obtained from XIX with aldehydes or ketones. This should be the case if the hydroxyl group at the bridge position in XIX were sterically disposed as shown for the corresponding lactam in B′, Fig. 1. Molecular models suggest the chair–boat conformation B′, Fig. 1, with the heterocycle in the boat arrangement, as the least strained form of the 2-azabicyclo[3.3.1]nonane system XIX or XVIII. It should be noted that only one isomeric lactam XVIII was obtained in pure form regardless of the configuration of the monocyclic precursors. Formation of the *anti*-lactam XVIII (Fig. 1, B′) from compounds of the *cis–cis* series requires an epimerization of the carbon bearing the hydroxyl group. The hydroxyl group in XVIII is in an axial conformation relative to the homocycle, a position which in the 3-oxabicyclo[3.3.1]nonane system has been found[26] to give rise to a more stable isomer than the equatorial position.

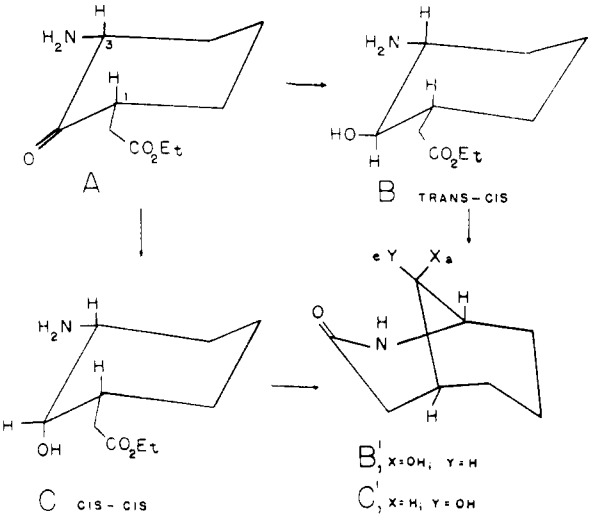


Fig. 1.

Discussion.—A comparison between the *trisubstituted* cyclohexane derivatives of the present study and the three *disubstituted* systems discussed in the Introduction (*cf.* i, ii, iii and iv) reveals some significant differences:

(1) *cis–cis*-3-Benzamido-2-hydroxycyclohexaneacetic acid (XIVb) appears to be considerably more reluctant to form a lactone than the analogous *cis*-2-hydroxycyclohexaneacetic acid.[8] Examination of Fig. 1 (C, free acid, N-benzoyl derivative) suggests two possibilities for lactone formation: (a) one, in which two groups would occupy equatorial positions (C_1–C_3) with the third group (C_2–OH) adopting an axial position; (b) a second possibility in which two groups (C_1–C_3) would be in axial positions, while the third group (C_2–OH) adopts an equatorial conformation. We assume that situation (a) leads to a more favorable transition state[4a,e] and ascribe the stability of hydroxy acid XIVb (relative to *cis*-2-hydroxycyclohexaneacetic acid) to the axial nature prescribed for the hydroxyl group by the presence of a bulky N-benzoylamino group at C_3.[27] The stability of the *cis–cis* series toward lactone formation is reflected also in the behavior of the amino alcohol ester XVb and in the amino alcohol acid XXIb. In the latter case XXIb the zwitterion character of the molecule also has to be considered.

(2) The different behavior on heating of *trans–cis*-ethyl 3-amino-2-hydroxycyclohexaneacetate (XVa) and *cis–cis*-ethyl 3-amino-2-hydroxycyclo-

boiling point of the respective pairs. The resolvable, hence *trans*-, 3,5-dimethylcyclohexanone has the higher refractive index of the isomeric pair and thus appears, as expected, to be the less stable form (J. von Braun and E. Anton, *Ber.*, **60**, 2438 (1927)). When two groups are vicinal the preponderance of equatorial molecules expected on purely steric grounds may be altered by electrostatic interactions, as in the α-halocyclohexanones (E. J. Corey, THIS JOURNAL, **75**, 2301 (1952)). In the amino ketone hydrochloride (A-HCl; Fig. 1) the strong dipoles in close proximity are not mutually repulsive.

(23) Reduction of 2-methylcyclohexanone in 50% aqueous acetic acid, reportedly gave *cis*-2-methylcyclohexanol in 75% yield; hydrogenation under neutral conditions gave *trans*-2-methylcyclohexanol in 65% yield (A. Skita and W. Faust, *Ber.*, **64**, 2878 (1931)). Catalytic reduction of 2-oxocyclohexaneacetic *acid*[8] in ethanol gave 84% of the lactone of *cis*-2-hydroxycyclohexaneacetic *acid* and 8% of *trans*-2-hydroxycyclohexaneacetic acid.

(24) It should be noted that *trans*-2-aminocyclohexanol (and most of its derivatives) melts lower than the *cis* isomer,[8] in disagreement with the Auwers–Skita rules. This seems to be the case for the amino alcohol esters.

(25) *Cf.* A. E. Hardegger and H. Ott, *Helv. Chim. Acta*, **36**, 1186 (1953), for the configuration of nor-pseudotropine.

(26) (a) D. H. R. Barton and G. A. Schmeidler, *J. Chem. Soc.*, 1197 (1948); (b) s 232 (1949).

(27) One of the rules of conformational analysis most frequently stressed (ref. 3a) regards an axial hydroxyl as being considerably more hindered—at least in intermolecular esterification—than an equatorial hydroxyl. The implication of these observations would appear to be that in *cis*-2-hydroxycyclohexaneacetic acid (*cis*-ii, R = H), which defies attempt at isolation due to ready lactonization, the OH group is capable of adopting an equatorial-type of conformation in the cyclization transition state, with the acetic acid side chain in an axial-like position.

hexaneacetate (XVb), both of which possess a *cis* arrangement of the amino group at C_3 and the ethyl acetate side chain at C_1, requires an explanation. As stated above, the simpler system lacking the hydroxyl group (iii) was found to undergo ready cyclization on heating.[6,7] Examination of molecular models (*cf.* Fig. 1) reveals that cyclization to a lactam in the *trans–cis* series (structure B) involves the close approach of 1,3-diaxial groups while the C_2–OH becomes axial. Cyclization to a lactam in the *cis–cis* series (structure C) involves again 1,3-diaxial groups but now with the C_2–OH in an equatorial position. In this latter arrangement, a close proximity between the equatorial hydroxyl at C_2 and the axial side chain at C_1 is observed; this situation might hinder the formation of the lactam and could permit competing *intermolecular* reactions of type $-CO-OC_2H_5/NH_2$ or $-COOC_2H_5/OH$.

The zwitterion character of *cis–cis*-3-amino-2-hydroxycyclohexaneacetic acid (XXIb) should markedly affect the conformation of the molecule as well as the ability of the groups to engage in intermolecular reactions; this could account for the successful cyclization of XXIb, with concomitant C_2-epimerization, to XVIII.[28]

An alternate explanation, along lines suggested by a Referee, may be that a *cis*-lactone is indeed formed from *cis–cis*-ethyl 3-amino-2-hydroxycyclohexaneacetate (XVb) on heating, but subsequently undergoes *intermolecular* reaction to amide. On this basis, the cyclization of amino acid XXIb to lactam XVIII would be possible, since lactone formation is unlikely in the zwitterion XXI. The cyclization of the acetate salt XXIIb to lactam XVIII could involve a transesterification to ethyl acetate and amino acid XXIb followed by cyclization to XVIII.

(3) All efforts to detect differences in the composition of the carbonyl products obtained from either *trans–cis* or *cis–cis*-ethyl 3-amino-2-hydroxycyclohexaneacetate (XVa and XVb) and nitrous acid were unsuccessful. Examination of the 2,4-dinitrophenylhydrazone derivative from the crude nitrosation products by chromatography and ultraviolet spectroscopy, and comparison with known mixtures of ethyl 2-formylcyclopentaneacetate (XVII) and ethyl 2-oxocyclohexaneacetate (as 2,4-dinitrophenylhydrazones) revealed only the presence of the product of ring contraction, XVII. This is in contrast to the results on the 2-aminocyclohexanols (iv) already mentioned.[11] We interpret the difference in terms of the relative energies of the possible transition states involved in the nitrosation[12] of *cis*-2-aminocyclohexanol and of *cis–cis*-ethyl 3-amino-2-hydroxycyclohexaneacetate (XVIb) (*cf.* Fig. 1, structure C). In XVIb the transition state for hydrogen migration (and formation of ethyl 2-oxocyclohexaneacetate) would involve an axial-type position for the ethyl acetate side chain at C_1; this feature is, of course, absent in the simpler *cis*-2-aminocyclohexanol. In the latter, but not in XVIb, the transition states for hydrogen migration and for ring contraction are, apparently, of comparable energies.

(4) Attempts to effect N → O acyl migrations on *trans–cis*- and *cis–cis*-3-benzamido-2-hydroxycyclohexaneacetic acids (XIVa and XIVb) utilizing hydrogen chloride in dioxane solution failed. This is presumably due to the participation of the acetic acid side chain in lactone formation under these conditions. From the *cis–cis* isomer XIVb a non-crystallizable product was obtained which exhibited in the infrared sharp bands at 5.65 μ (lactone) and 6.10 μ (amide) but lacked the carboxyl band at 5.9 μ.

Acknowledgment.—We are grateful to Research Corporation for grants in support of this work.

Experimental[29]

Ethyl 1-Carbethoxy-2-oxocyclohexaneacetate (I).[30]—To a well-stirred mixture of finely divided sodium (13.5 g.) and dry benzene (500 ml.) was added, in one portion, 100 g. of 2-carbethoxycyclohexanone.[31] The mixture was refluxed for 2.5 hr. and then treated with 100 g. (67 ml.) of ethyl bromoacetate, added dropwise during reflux. The resulting solution was heated further for 5 hr. and then cooled to room temperature. Addition of 250 ml. of 5% sulfuric acid yielded an organic layer which was washed successively with dilute sulfuric acid, sodium bicarbonate and water and dried over sodium sulfate. The oil which remained after removal of the solvent *in vacuo* was fractionated through a four-inch Vigreux column, yielding (in addition to 5 g. of recovered 2-carbethoxycyclohexanone and 4 g. of impure material, b.p. 90–138° at 3.4 mm.) three fractions, b.p. 139–143° (3.4 mm.), $n^{25}D$ 1.4606–1.4610. This clear colorless oil (98.7 g., 70% yield) gave no color with alcoholic ferric chloride and did not absorb in the ultraviolet (220–380 mμ) to a significant extent in concentrations as high as 0.620 g. per liter (EtOH). For analysis a sample was redistilled: b.p. 135° (1.1 mm.), $n^{25}D$ 1.4605.

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.9; H, 7.9. Found: C, 60.8; H, 7.9.

The 2,4-dinitrophenylhydrazone, which formed with difficulty, was obtained as yellow plates, m.p. 99.5–100.0° (methanol).

Anal. Calcd. for $C_{19}H_{24}N_4O_8$: C, 52.3; H, 5.5; N, 12.8. Found: C, 52.3; H, 5.4; N, 12.7.

Ethyl 3-Bromo-1-carbethoxy-2-oxocyclohexaneacetate.—A cooled solution of ethyl 1-carbethoxy-2-oxocyclohexaneacetate (I) (10.0 g.) in chloroform (100 ml.) was treated with a solution of bromine (6.25 g.) in chloroform (75 ml.). The solution was stirred 15 minutes at 0° and 1 hr. at room temperature. The washed chloroform solution was concentrated *in vacuo* yielding an oil ($n^{25}D$ 1.4885) which on distillation afforded the bromoketone as a clear viscous oil (8.78 g., 67% yield), b.p. 135–138° (0.1 mm.), $n^{25}D$ 1.4905.

Anal. Calcd. for $C_{13}H_{19}O_5Br$: C, 46.6; H, 5.7; Br, 23.8; Found: C, 46.5; H, 5.6; Br, 23.7.

On prolonged standing the oil crystallized; m.p. 54.5–

(28) Participation of the amino group in intermolecular reactions is perhaps avoided also, at least at relatively low temperatures, by formation of the acetate salt as in XXIIb. It is of interest that the acetate salt XXIIb can be sublimed unchanged at 85° and 0.1 mm. while pyrolysis at 160° and atmospheric pressure resulted in lactam XVIII. The yield of XVIII from XXIIb was much poorer at 135° or at 200°.

(29) Analyses by Micro-Tech Laboratories, Skokie, Ill., and Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(30) The preparation of I and II has been reported (N. N. Chatterjee, A. Bose and H. B. Roy, *J. Indian Chem. Soc.*, **24**, 169 (1947)); the materials were not fully characterized as to physical properties and degree of purity (*cf.* formation of III). I has been prepared in 31% yield (E. H. Charlesworth, J. A. McRae and H. H. McFarlane, *Can. J. Research*, **21B**, 55 (1943)). See also P. Sen-Gupta and B. K. Bhattacharyya, *J. Indian Chem. Soc.*, **31**, 337 (1954). In a recent publication physical constants for II were recorded (N. J. Leonard and W. J. Middleton, THIS JOURNAL, **74**, 5114 (1952)).

(31) H. R. Snyder, L. A. Brooke and S. H. Shapiro, in A. H. Blatt, Editor, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 531. Redistilled material, b.p. 86–88° (3.2 mm.), $n^{25}D$ 1.4760, was used.

56.0° (petroleum ether). Found: C, 46.8; H, 5.7; Br, 24.0.

Experiments with Ethyl 3-Bromo-1-carbethoxy-2-oxocyclohexaneacetate.—Preliminary attempts to convert the bromoketone into an aminoketone, utilizing potassium phthalimide, hexamethylenetetramine or ammonia were unpromising.

Treatment of the bromoketone with sodium azide in aqueous ethanol gave (in 75% yield) a non-crystallizable azidoketone exhibiting the characteristic 4.7 μ band of azides in the infrared. Hydrogenation of the azidoketone with palladium-on-carbon in ethanol solution gave ethyl 1-carbethoxy-2-oxocyclohexaneacetate (I) in good yield as the sole isolable product.

Ethyl 3-Carbethoxy-2-oxocyclohexaneacetate (II).[30,32]—To a solution prepared from anhydrous ethanol (60 ml.) and sodium (4.6 g.) was added, in one portion, 45.3 g. of ethyl 1-carbethoxy-2-oxocyclohexaneacetate (I). After a reflux period of 8 hours, the alcohol was removed *in vacuo*. The remaining oil was treated with ice-cold 5% sulfuric acid (150 ml.) and extracted with ether. The washed and dried ether extract yielded 33.7 g. of oil on evaporation. Distillation through a 3 × 1.5-inch Vigreux column at 1 mm. gave the following fractions: (a) b. p. to 146.5°, 2.1 g., $n^{25}D$ 1.4720; (b) b. p. 137–139°, 19.7 g., $n^{25}D$ 1.4701; (c) b. p. 140–141°, 4.5 g., $n^{25}D$ 1.4682; (d) b. p. 141° and up, 2.8 g., $n^{25}D$ 1.4653.

All fractions gave a deep purple color with alcoholic ferric chloride. The yield of ketodiester II based on fractions b and c was 54%. In several runs yields of 54–59% were realized. Refractive indices at 25° varied in the range 1.4717–1.4682, depending on the proportion of enol present. Aged samples (2.5 months) had $n^{25}D$ 1.4688. The material absorbed strongly[33] at 258 mμ; ϵ values in the range of 2,870 and 7,500 (EtOH) were obtained in a number of fractions of different enol content. In alkaline solution (1:1 EtOH–0.1 *N* sodium hydroxide) the ketodiester II had $\lambda_{max.}$ 288 mμ, ϵ 11,300.

For analysis the combined b and c fractions described above were redistilled to yield material of b.p. 134° (0.85 mm.), $n^{25}D$ 1.4701.

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.9; H, 7.9. Found: C, 60.8; H, 8.0.

The 2,4-dinitrophenylhydrazone was obtained in quantitative yield, m.p. 75–82° (crude). The analytical sample had m.p. 85.4–86.0° (orange needles from methanol).

Anal. Calcd. for $C_{19}H_{24}N_4O_8$: N, 12.8. Found: N, 12.7.

2-Oxocyclohexaneacetic Acid from Ketodiester I and II.—Both ethyl 1-carbethoxy-2-oxocyclohexaneacetate (I) and ethyl 3-carbethoxy-2-oxocyclohexaneacetate (II) were degraded to 2-oxocyclohexaneacetic acid in *ca.* 80–85% yield upon heating with acetic acid–concentrated hydrochloric acid (1:1).

2-Oxocyclohexaneacetic Acid 2,4-Dinitrophenylhydrazone, m.p. 202–203° (methanol), was prepared in aqueous solution using 2,4-dinitrophenylhydrazinium chloride.

Anal. Calcd. for $C_{14}H_{16}N_4O_6$: C, 50.0; H, 4.8. Found: C, 50.5; H, 4.8.

Methyl 2-oxocyclohexaneacetate 2,4-dinitrophenylhydrazone, m.p. 138–139° (methanol–ethyl acetate), was prepared from the keto acid in methanol solution using 2,4-dinitrophenylhydrazinium sulfate.

Anal. Calcd. for $C_{15}H_{18}N_4O_6$: C, 51.4; H, 5.2. Found: C, 51.5; H, 5.3.

Ethyl 2-oxocyclohexaneacetate 2,4-dinitrophenylhydrazone was prepared from ethyl 2-oxocyclohexaneacetate as orange-yellow needles, m.p. 130.4–131.2° (ethyl acetate–methanol); $\lambda^{CHCl_3}_{max.}$ 365 mμ, ϵ 24,300.

Anal. Calcd. for $C_{16}H_{20}N_4O_6$: C, 52.7; H, 5.5; N, 15.4. Found: C, 52.1; H, 5.4; N, 15.6.

2-Oxocyclohexaneacetic acid oxime, m.p. 143.0–143.4° (ethyl acetate).

Anal. Calcd. for $C_8H_{13}O_3N$: C, 56.1; H, 7.6; N, 8.2. Found: C, 55.9; H, 7.7; N, 8.2.

1,2,6-Tricarbethoxyhexane (III) from Ethyl 1-Carbethoxy-2-oxocyclohexaneacetate (I).—When the keto ester I was kept at room temperature with 4% ethanolic sodium ethoxide for 24 hours variable amounts of an oil, b.p. 150–153° (1.5 mm.), $n^{25}D$ 1.4396, were obtained. The oil gave no carbonyl derivatives.

Anal. Calcd. for $C_{15}H_{26}O_6$: C, 59.5; H, 8.6. Found: C, 59.1; H, 8.7.

3-Carbethoxy-2-oxocyclohexaneacetic Acid (Keto Form IV).—A solution of 10.0 g. of potassium hydroxide in 50 ml. of anhydrous ethanol was added to 10.0 g. of ethyl 3-carbethoxy-2-oxocyclohexaneacetate (II) and the mixture was kept at room temperature for 1.5 hours. The precipitate formed was filtered, washed with anhydrous ethanol and ether, and dissolved in water (15 ml.). The ice-cold solution was treated slowly with 14 ml. of a 1:1 mixture of concentrated hydrochloric acid and water. The oily precipitate which formed crystallized on standing; yield 4.55 g. (51%), m.p. 106–108°; neutral equivalent calcd. 228, found 226. The analytical sample of IV was obtained as white needles, m.p. 107–108° (water). The keto acid was very slightly soluble in hexane and gave with aqueous ferric chloride a faint red color, which deepened markedly on standing.

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.8; H, 7.1. Found: C, 57.5; H, 7.2.

Ultraviolet Absorption Data.—The keto acid IV showed no appreciable absorption at 258 mμ in 95% ethanol after 13, 45, 60 and 88 minutes. After 10 hours the ϵ value was 1630, after 46 hours ϵ was 2070; in alkaline medium (1:1 95% EtOH–0.1 *N* NaOH): $\lambda_{max.}$ 288 mμ, ϵ 9,060. The infrared absorption spectrum in Nujol mull showed bands at 5.78 and 5.85–5.90 μ.

3-Carbethoxy-2-oxocyclohexaneacetic Acid 2,4-Dinitrophenylhydrazone (DNP of IV).—This compound, m.p. 167.7–169.1° (yellow-orange plates from methanol), was obtained from the keto acid IV in hot acetic acid using 2,4-dinitrophenylhydrazine.

Anal. Calcd. for $C_{17}H_{20}N_4O_8$: C, 50.0; H, 4.9; N, 13.7. Found: C, 50.3; H, 5.0; N, 13.5.

Ethyl 3-carbethoxy-2-oxocyclohexaneacetate 2,4-dinitrophenylhydrazone (DNP of II), m.p. 85–86°, alone and mixed with an authentic sample, resulted when a solution of the keto acid IV in ethanol was carefully treated with 2,4-dinitrophenylhydrazinium sulfate. More drastic conditions may lead to the formation of 2-oxocyclohexaneacetic acid 2,4-dinitrophenylhydrazone.

Action of Hydrazine on the Keto Acid IV.—When a solution of the keto acid IV in ethanol was refluxed with 95% hydrazine, a crystalline product VI, m.p. 248–249°, was obtained. This material was soluble in dilute sodium bicarbonate and dilute hydrochloric acid and gave a deep red color with alcoholic ferric chloride. The analytical sample of VI had m.p. 249–250° (aqueous ethanol) and $\lambda^{EtOH}_{max.}$ 252 mμ.

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.1; H, 6.2: Found. C, 55.6; H, 6.4.

3-Carbethoxy-2-oxocyclohexaneacetic Acid (Enol Form V).—A solution of the keto acid IV, m.p. 106–108° (1.00 g.), in 10 ml. of glacial acetic acid containing 1 ml. of boron trifluoride etherate was allowed to stand at room temperature and then poured into water. The crystalline product which precipitated was collected and dried *in vacuo*. The material (0.63 g.) softened at 74°, melted at 75.5–77.0°, resolidified at 80–85° and remelted at 106–108°. The material gave an *instantaneous* deep red color with alcoholic ferric chloride and decolorized bromine at once. The enol V was dissolved in an excess of hexane, the solution filtered and concentrated to a small volume until crystals began to form. The analytical sample so obtained had m.p. 75.5–76.0°.

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 57.8; H, 7.1. Found: C, 58.3; H, 7.4.

On prolonged boiling in hexane, without intervening filtration, a conversion of the low melting V into the higher melting IV was observed.

Ultraviolet Absorption Data.—Freshly prepared solutions of the enol form V (m.p. 76°) in 95% ethanol had the following ϵ values at 258 mμ: 9,040 after 13 minutes, 6,450

(32) The course of the rearrangement seemed to be markedly affected by the concentration of the base used.

(33) For comparison the ultraviolet spectrum of a purified sample of 2-carbethoxycyclohexanone (footnote 28 and R. Schreck, THIS JOURNAL, **71**, 1881 (1949)) was examined: λ^{EtOH}_{max} 258 mμ, ϵ 10,100; in 1:1 EtOH–0.1 *N* sodium hydroxide: λ_{max} 288 mμ, ϵ 13,300.

after 42 minutes, 3,300 after 10 days. In alkaline solution (1:1 ethanol–0.1 *N* NaOH) the material V, m.p. 76°, had $\lambda_{max.}$ 288 mμ, ε 8,330.

Infrared Absorption Data.—A sample of material V, m.p. 76°, mulled in Nujol, exhibited a spectrum which was very similar, but not identical, to that described for the Nujol mull of the keto form IV.

$\Delta^{1(9)}$-9-Carbethoxy-3-oxo-2-oxabicyclo[4.3.0]nonane (VII).—A solution of 3-carbethoxy-2-oxocyclohexaneacetic acid (IV) (2.09 g.) in acetic anhydride (50 ml.) was allowed to stand at room temperature for 14 hours. The crystalline material which remained after removal of the acetic anhydride had m.p. 65–68° and represented a quantitative yield of the enol lactone VII. The analytical sample had m.p. 67.8–68.5° (white needles from hexane), $\lambda_{max.}^{EtOH}$ 234 mμ, ε 7320, strong bands at 5.50 and 5.82–5.86 μ. The enol lactone VII was insoluble in dilute sodium bicarbonate solution, gave no immediate color with alcoholic ferric chloride and decolorized bromine with difficulty.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.8; H, 6.7. Found: C, 62.9; H, 6.9.

The enol lactone VII was recovered unchanged from a solution in ethanol which had stood at room temperature for 12 hours. When a drop of sulfuric acid was added to the ethanolic solution, the resulting product was an oil identified as ethyl 3-carbethoxy-2-oxocyclohexaneacetate (II) on the basis of ultraviolet spectra and derivatives.

The enol lactone was also obtained from the keto acid IV on evaporative distillation at 86° (1.4 mm.).

***cis*-3-Carbethoxycyclohexaneacetic Acid (VIII).**—A solution of the enol lactone VII (8.89 g.) in anhydrous ethanol (100 ml.) was hydrogenated (11 p.s.i.) in the presence of platinum oxide catalyst for 2.5 hr. Removal of the solvent after filtration gave 7.93 g. (87%) of crude acid ester, $n^{27}D$ 1.4664. The crude material was dissolved in 10% aqueous sodium bicarbonate (50 ml.) and the solution was extracted with ether. Acidification of the aqueous layer with hydrochloric acid, extraction with ether and removal of the ether yielded 7.56 g. of oil from which was obtained 5.59 g. (61%) of *cis*-3-carbethoxycyclohexaneacetic acid (VIII), b.p. 127–130° (0.1 mm.), $n^{27}D$ 1.4658; neutral equivalent calcd. 214, found 215; bands at 5.81 and 5.89 μ (CCl_4).

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.7; H, 8.5. Found: C, 61.3; H, 8.6.

The crude hydrogenation product exhibited an infrared spectrum lacking the characteristic lactone band.

Alkaline hydrolysis of the acid ester VIII gave *cis*-3-carboxycyclohexaneacetic acid (IX) identified by mixed melting point with an authentic sample previously prepared.[15]

When *cis*-3-carbethoxycyclohexaneacetic acid (VIII) was refluxed with excess hydrazine (95%) for 24 hours the **dihydrazide**, m.p. 252.8–253.6° (ethanol–water), was obtained.

Anal. Calcd. for $C_9H_{18}N_4O_2$: C, 50.5; H, 8.5; N, 26.1. Found: C, 50.8; H, 8.5; N, 25.7.

3-Carbethoxy-2-oxocyclohexaneacetic Acid (IV) From Ethyl 1-Carbethoxy-2-oxocyclohexaneacetate (I) without Isolation of Intermediates.—The keto ester I (110 g.) was added to a solution of sodium ethoxide in ethanol (from 11 g. of sodium and 137 ml. of anhydrous ethanol) under reflux. After 6 hours at its reflux temperature the mixture was cooled to room temperature and poured into a solution of potassium hydroxide (91 g. of 85% KOH pellets) in anhydrous ethanol (455 ml.). The precipitate formed was filtered, washed with ether and added in small portions to cold aqueous hydrochloric acid (90 ml. of concentrated hydrochloride in 90 ml. of water). The solid was filtered and triturated with benzene (150 ml.); concentration of the benzene solution gave 10.5 g. of keto acid IV, m.p. 102–104°, followed by a second crop (2.7 g., m.p. 83–100°).

The aqueous filtrate obtained above was kept in the icebox and deposited 25.9 g. of additional keto acid IV, m.p. 103–105°. The total yield was 39.1 g. (40%).

An oil, extractable with ether, and not further investigated also was found in the aqueous layer (14.5 g., b.p. 155–175° (1 mm.)).

3-Oximino-2-oxocyclohexaneacetic Acid (XI).—To a solution of potassium hydroxide (9.8 g. of 85% KOH pellets) and sodium nitrite (3.47 g.) in water (155 ml.), kept at 0°, was added 11.3 g. of 3-carbethoxy-2-oxocyclohexaneacetic acid (IV). The addition was performed with efficient stirring and in a *nitrogen atmosphere*. After 1.5 hours at 0°, the yellow solution was saturated with sodium chloride and acidified with ice-cold sulfuric acid (5.4 ml. of concentrated acid in 20 ml. of water). The colorless crystalline precipitate formed in the cold solution was filtered and dried; yield 5.10 g. (56%), m.p. 131° dec.

Extraction of the aqueous filtrate obtained above with ten 100-ml. portions of ether gave an additional 1.25 g. (14%) of oximino ketone XI. 3-Oximino-2-oxocyclohexaneacetic acid (XI) was appreciably soluble in ethanol and *n*-butyl alcohol, moderately soluble in water and ether and very sparingly soluble in benzene, chloroform and carbon tetrachloride. The oximino ketone gave a deep green color with ethanolic ferric chloride and readily dissolved in dilute sodium bicarbonate. Solutions of the oximino ketone *rapidly deteriorated on standing*. The analytical sample of XI had m.p. 136.5–136.8° dec. (from ether upon cooling to −78°) and exhibited bands at 5.88 and 5.98 μ (Nujol mull).

Anal. Calcd. for $C_8H_{11}O_4N$: C, 51.9; H, 6.0; N, 7.6. Found: C, 52.0; H, 6.0; N, 7.7.

***cis*-Ethyl 3-amino-2-oxocyclohexaneacetate Hydrochloride (XII).**—To a solution of 3-oximino-2-oxocyclohexaneacetic acid (XI) (0.990 g.) in anhydrous ethanol (10 ml.) was added 3 ml. of a solution of hydrogen chloride in anhydrous ethanol (titer: 0.00535 mole of base per ml. of solution). The hydrogenation was carried out at atmospheric pressure for 17 hours in the presence of 10% palladium-on-charcoal (0.20 g.). A maximum hydrogen uptake of 190 ml. (or 77% of the theoretical based on two moles of hydrogen) was observed. Removal of the catalyst by filtration and of the solvent by distillation *in vacuo*, gave a yellow oil which crystallized on trituration with ethyl acetate; yield 0.670 g. (53%), m.p. 115–120°. The analytical sample of XII had m.p. 136.4–137.6° (ethyl acetate) and exhibited bands at 4.93 and 5.83 μ (Nujol mull).

Anal. Calcd. for $C_{10}H_{18}O_3NCl$: C, 50.1; H, 7.7; N, 5.9; Cl, 15.0. Found: C, 50.4; H, 7.5; N, 6.0; Cl, 15.0.

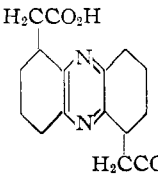
***cis*-Ethyl 3-benzamido-2-oxocyclohexaneacetate (XIII)** was obtained directly from the hydrochloride XII on treatment with benzoyl chloride and 10% aqueous sodium bicarbonate at room temperature overnight. The benzamide, had m.p. 97.2–98.2° (benzene–petroleum ether) and bands at 2.94, 5.80, 5.86 and 6.04 μ (carbon tetrachloride).

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.3; H, 7.0; N, 4.6. Found: C, 67.4; H, 7.1; N, 4.6.

***cis*-Ethyl 3-Amino-2-oxocyclohexaneacetate Hydrochloride (XII) from Ethyl 3-Carbethoxy-2-oxocyclohexaneacetate (II) without Purification of Intermediates.**—Ethyl 3-carbethoxy-2-oxocyclohexaneacetate (II) (31.7 g.) was nitrosated as described above using 15.3 g. of sodium hydroxide, 8.50 g. of sodium nitrite and 300 ml. of water. The total reaction time was 21 hours. Acidification of the resulting yellow solution with 11.5 ml. of concentrated sulfuric acid in 75 ml. of water was followed by extraction with eight 50-ml. portions of *n*-butyl alcohol. The combined butanol extracts were washed with water, dried over magnesium sulfate and evaporated to dryness *in vacuo*. The semi-solid residue was dissolved in 40 ml. of anhydrous ethanol and the solution treated with 60 ml. of a solution obtained by saturation of ethanol with hydrogen chloride. The hydrogenation was carried out at an initial pressure of 34 p.s.i. in the presence of palladium-on-charcoal (4.0 g.) during 3.5 hours. The product was worked up as before to yield an initial amount of hydrochloride (4.75 g.) melting at 113–16°. The filtrate from the crystallization was evaporated to dryness and the residue was dissolved in ethanol containing hydrogen chloride. Removal of the solvent after standing overnight gave a residue which was triturated with ethyl acetate, affording 3.50 g. of additional hydrochloride of m.p. 119–125°. The total yield of hydrochloride XII suitable for further work was 43% based on ethyl 3-carbethoxy-2-oxocyclohexaneacetate (II).

When the amino keto ester hydrochloride XII was treated with aqueous sodium bicarbonate a solid, m.p. 200–202° (ethyl acetate) formulated as the octahydrophenazine derivative was obtained.

Anal. Calcd. for $C_{16}H_{20}O_4N_2$: C, 63.1; H, 6.6; N, 9.2. Found: C, 62.9; H, 6.5; N, 9.3.



Catalytic Hydrogenation of *cis*-Ethyl 3-Benzamido-2-oxocyclohexaneacetate (XIII). *trans-cis*-3-Benzamido-2-hydroxycyclohexaneacetic Acid (XIVa).—A solution of *cis*-ethyl 3-benzamido-2-oxocyclohexaneacetate (XIII) (0.262 g.) in anhydrous ethanol (10 ml.) was hydrogenated at room temperature and atmospheric pressure in the presence of 0.011 g. of platinum oxide. Removal of the catalyst and of the solvent left a residue which was treated at room temperature with 10 ml. of a 5% aqueous solution of sodium hydroxide. After 4 hr. the solution was extracted with ether and acidified yielding 0.094 g. of solid, m.p. 195–202°. One recrystallization from ethanol–benzene gave 0.068 g. of XIVa, m.p. 213.5–215°; bands at 3.04, 5.93 and 6.16 μ (KBr).

Anal. Calcd. for $C_{15}H_{19}O_4N$: C, 65.0; H, 6.9; N, 5.0. Found: C, 64.5; H, 6.9; N, 4.3.

When a solution of *trans-cis*-3-benzamido-2-hydroxycyclohexaneacetic acid (XIVa) in dioxane was allowed to stand at room temperature for 0.5 hr. a product of complex infrared spectrum was obtained. The spectrum had broad and ill-defined bands at 5.5–5.6 μ and 5.8–5.9 μ in addition to a band at 6.05 μ. When the reaction time was increased to 5.5 hr. a change in the infrared spectrum of the product was noted. In this case a sharp band at 5.65 μ was present accompanied by a broad band at 5.88–5.93 μ.

***trans-cis*-Ethyl 3-amino-2-hydroxycyclohexaneacetate (XVa).**—To a solution of *cis*-ethyl 3-amino-2-oxocyclohexaneacetate hydrochloride (XII) (1.00 g.) in anhydrous ethanol (10 ml.) cooled to 0° was added in small portions 0.324 g. of sodium borohydride. Following a 2.5-hr. shaking period at room temperature, water (10 ml.) was added, the solution was saturated with sodium chloride and extracted with ether. Removal of the ether left an oil (0.617 g., 73% yield) which was triturated with petroleum ether. Concentration of the petroleum ether extract to a small volume (5 ml.) afforded 0.310 g. (36%) of colorless crystalline amino alcohol ester XVa, m.p. 67–70°. The analytical sample of XVa, had m.p. 76.5–77.5° (petroleum ether), bands at 3.04–3.06, 3.18–3.22 and 5.82 μ (CCl_4).

Anal. Calcd. for $C_{10}H_{19}O_3N$: C, 59.7; H, 9.5; N, 7.0. Found: C, 59.9; H, 9.5; N, 7.0.

When the reduction was run for 0.5 or 14 hours no crystalline material was obtained. No amino alcohol ester could be obtained from the petroleum ether-insoluble residues obtained as described above.

***trans-cis*-Ethyl 3-amino-2-hydroxycyclohexaneacetate Hydrochloride (XVIa).**—The hydrochloride was prepared from an ether solution of the amino ester XVa upon treatment with hydrogen chloride. XVIa had m.p. 125–126° (ethyl acetate).

Anal. Calcd. for $C_{10}H_{20}O_3NCl$: C, 50.5; H, 8.5; N, 5.9. Found: C, 50.6; H, 8.5; N, 5.5.

***trans-cis*-3-Benzamido-2-hydroxycyclohexaneacetic Acid (XIVa).**—A mixture of *trans-cis*-ethyl 3-amino-2-hydroxycyclohexaneacetate (XVa) (0.362 g.), 5% aqueous sodium hydroxide (9 ml.) and benzoyl chloride (0.3 ml.) was shaken at room temperature for 3 hr. The solution was extracted with ether and acidified yielding a precipitate from which 0.134 g. (23%) of XIVa, m.p. 207–209°, was obtained after one recrystallization from ethanol–benzene. This material was identical with XIVa previously prepared.

***anti*-9-Hydroxy-3-oxo-2-azabicyclo[3.3.1]nonane (XVIII).**—*trans-cis*-Ethyl 3-amino-2-hydroxycyclohexaneacetate (XVa) (0.200 g.) was heated at 150–160° for 45 minutes. The product was sublimed (160–200°, 0.3 mm., 4 hr.) to yield 0.155 g. (95%) of colorless, crystalline material, m.p. 206–210° (approx.). One recrystallization from ethyl acetate–ethanol gave 0.107 g. (69%) of XVIII, m.p. 241–243°. Analytically pure XVIII (0.088 g., 57%), m.p. 251–253°, was obtained after one more recrystallization. XVIII had bands at 3.05 and 3.22 μ (perfluorokerosene mull) and 6.13 μ (Nujol mull), was soluble in water and ethanol and sparingly soluble in chloroform, carbon tetrachloride, ethyl acetate and benzene.

Anal. Calcd. for $C_9H_{13}O_2N$: C, 61.9; H, 8.4; N, 9.0; mol. wt., 155. Found: C, 61.6; H, 8.2; N, 9.0; mol. wt., 164.

A sample of XVIII (m.p. 251–253°) heated at 255° for 5 minutes remelted at 203°–.

***anti*-9-Hydroxy-2-azabicyclo[3.3.1]nonane (XIX).**—*anti*-9-Hydroxy-3-oxo-2-azabicyclo[3.3.1]nonane (XVIII) (1.00 g.) was added in small portions to a stirred suspension of lithium aluminum hydride (0.80 g.) in anhydrous ether (150 ml.) in a nitrogen atmosphere. The mixture was refluxed for 24 hours and stirred at room temperature for an additional 12 hours. Moist ether was added, the mixture was filtered and the solid collected was washed with chloroform. The solid was treated with 0.1 *N* sodium hydroxide and the mixture extracted with chloroform. A solid residue, which was still present, was dried over phosphorus pentoxide and extracted with warm chloroform. The various chloroform extracts were combined with the original ether layer and the solution evaporated to dryness. Recrystallization of the residue (0.75 g.) from ethyl acetate, followed by evaporative distillation at 120° (0.3 mm.) and one final recrystallization from the same solvent afforded 0.132 g. (23%) of pure amino alcohol XIX, m.p. 204.5–206.5°, bands at 2.90–2.97 and 3.22 μ (Nujol mull).

Anal. Calcd. for $C_8H_{15}O$: C, 68.0; H, 10.7; N, 9.9. Found: C, 68.3; H, 10.7; N, 9.9.

The picrate of XIX, prepared in chloroform solution, had m.p. of 238.2–239.0° (fine yellow needles from ethyl acetate).

Anal. Calcd. for $C_{14}H_{18}O_8N_4$: N, 15.1. Found: N, 15.2.

Treatment of XIX with *p*-nitrobenzaldehyde gave no oxazolidine derivative.[24]

***cis-cis*-Ethyl 3-Amino-2-hydroxycyclohexaneacetate Hydrochloride (XVIb).**—A solution of *cis*-ethyl 3-amino-2-oxocyclohexaneacetate hydrochloride (XII) (3.0 g.) in water (15 ml.) was hydrogenated at atmospheric pressure in the presence of platinum oxide (0.30 g.). After 8.5 hr., when the theoretical amount of hydrogen had been consumed, the solution was filtered and evaporated to dryness, yielding 2.93 g. (97%) of colorless crystals, m.p. 130–155°. One recrystallization from ethyl acetate–ethanol gave 2.13 g. (71%) of hydrochloride XVIb, m.p. 164–167°. The analytical sample had m.p. 168–170° (fine needles from ethyl acetate–ethanol).

Anal. Calcd. for $C_{10}H_{20}O_3NCl$: C, 50.5; H, 8.5; N, 5.9. Found: C, 50.5; H, 8.4; N, 5.7.

Attempts to isolate an isomeric hydrochloride in crystalline form from this reaction were not successful.

***cis-cis*-Ethyl 3-amino-2-hydroxycyclohexaneacetate Acetate (XXIIb).**—A solution of *cis-cis*-ethyl 3-amino-2-hydroxycyclohexaneacetate hydrochloride (XVIb) (0.337 g.) in anhydrous ethanol (7 ml.) was treated at room temperature with a saturated solution of sodium acetate in anhydrous ethanol. The solution was filtered and evaporated to dryness *in vacuo*. The residue was dissolved in 40 ml. of ethyl acetate, filtered, concentrated to *ca.* 20 ml. and diluted with ligroin. On cooling, 0.250 g. (68%) of colorless crystals, m.p. 129–130°, was obtained. The analytical sample of the acetate salt XXIIb, obtained by sublimation at 85° (0.1 mm.), had m.p. 128.5–129.5°, the melt resolidified and remelted at *ca.* 202°. The salt was soluble in water and chloroform.

Anal. Calcd. for $C_{12}H_{23}O_5N$: C, 55.2; H, 8.9; N, 5.4. Found: C, 55.3; H, 8.6; N, 5.3.

Treatment of the acetate salt XXIIb with a solution of hydrogen chloride in anhydrous ethanol regenerated the hydrochloride XVIb.

***cis-cis*-Ethyl 3-Amino-2-hydroxycyclohexaneacetate (XVb).**—A solution of *cis-cis*-ethyl 3-amino-2-hydroxycyclohexaneacetate hydrochloride (XVIb) (0.787 g.) in anhydrous ethanol (10 ml.) was treated with one equivalent of potassium hydroxide in anhydrous ethanol. The filtered solution was evaporated to dryness at 50° *in vacuo*. The crystalline residue (0.540 g.) which melted at *ca.* 110°, was extracted with 20 ml. of boiling ethyl acetate. Concentration of the ethyl acetate filtrate to *ca.* 3 ml. afforded, after cooling, 0.357 g. of colorless crystals of the amino ester

XVb, m.p. 103–104°. The analytical sample had the same m.p. and exhibited bands at 2.96–3.01 and 5.82 mμ ($CHCl_3$).

Anal. Calcd. for $C_{10}H_{19}O_3N$: C, 59.7; H, 9.5; N, 7.0. Found: C, 59.9; H, 9.3; N, 7.2.

Pyrolysis of *cis–cis*-Ethyl 3-Amino-2-hydroxycyclohexaneacetate (XVb).—When the amino alcohol ester XVb was heated at 160–170° and the product submitted to an evaporative distillation, gums, which slowly changed into waxy solids, resulted. No hydroxy lactam XVIII could be obtained on attempted recrystallizations. The material showed pronounced bands at 5.8 and 6.1 μ and very slight absorption at 5.65 μ.

***cis–cis*-3-Amino-2-hydroxycyclohexaneacetic Acid Hydrochloride (XXb).** (a) **By Hydrolysis of Ester Amine Hydrochloride XVIb.**—A solution of *cis–cis*-ethyl 3-amino-2-hydroxycyclohexaneacetate hydrochloride (XVIb) (0.500 g.) in water (25 ml.) containing 2 ml. of 5% hydrochloric acid was refluxed for 12 hours. Evaporation to dryness gave 0.465 g. of crystals, m.p. 187–190°. Recrystallization from ethanol gave 0.227 g. of amino acid hydrochloride, m.p. 209–212°. The analytical sample of XXb had m.p. 216.5–217.5° (needles).

Anal. Calcd. for $C_8H_{16}O_3NCl$: C, 45.8; H, 7.6; N, 6.7. Found: C, 46.0; H, 8.0; N, 6.6.

(b) **By Hydrogenation of *cis*-Ethyl 3-Amino-2-oxocyclohexaneacetate Hydrochloride (XII).**—A solution of crude amino keto ester hydrochloride XII (39.6 g.) in water (100 ml.) containing 10 ml. of 5% hydrochloric acid was heated to its boiling point and treated with Norit for 20 minutes. The clear, filtered solution was cooled to room temperature and hydrogenated in the presence of 2.0 g. of platinum oxide (initial pressure 29 p.s.i.). After 12.2 hours, the solution was filtered and evaporated to dryness. A total of 34 g. of colorless crystals, m.p. 181–187°, resulted. Trituration of the crude with anhydrous ethanol (150 ml.) left 17.7 g., (51% yield) of insoluble amino acid hydrochloride XXb, m.p. 209–210°, suitable for further work.

***cis–cis* 3-Benzamido-2-hydroxycyclohexaneacetic Acid (XIVb).**—A mixture of *cis–cis*-3-amino-2-hydroxycyclohexaneacetic acid hydrochloride (XXb) (0.477 g.), 5% aqueous sodium hydroxide (6 ml.) and benzoyl chloride (0.3 ml.) was shaken at room temperature for one hour. Acidification with hydrochloric acid gave a solid from which 0.339 g. (53%) of XIVb, m.p. 166–168°, was obtained after one recrystallization from ethyl acetate. The analytical sample had m.p. 169.0–169.3° (ethyl acetate), bands at 2.95, 3.04, 5.93 and 6.16 μ (KBr).

Anal. Calcd. for $C_{15}H_{19}O_4N$: C, 65.0; H, 6.9; N, 5.0. Found: C, 65.3; H, 7.0; N, 4.8.

When a solution of *cis–cis*-3-benzamido-2-hydroxycyclohexaneacetic acid (XIVb) in dioxane containing hydrogen chloride was allowed to stand at room temperature for 0.5 hr. a non-crystallizable product was formed exhibiting a sharp and strong band at 5.65 μ (lactone) and 6.05 μ (amide) but no band at 5.9 μ (carboxyl or benzoate). No significant change in the appearance of the infrared spectrum of the product was observed when the reaction time was extended to 5.5 hr.

***cis–cis*-3-Amino-2-hydroxycyclohexaneacetic Acid (XXIb).**—A suspension of *cis–cis*-3-amino-2-hydroxycyclohexaneacetic acid hydrochloride (XXb) (0.500 g.) in 95% ethanol (20 ml.) was warmed 5 minutes with 15 ml. of a saturated solution of sodium acetate in 95% ethanol. The crystalline solid which separated was filtered, washed with ethanol and dried. The yield of amino acid XXIb, m.p. 232–234° dec., was 0.369 g. (96%). The analytical sample of XXIb had m.p. 237–238° (water–ethanol 1:30).

Anal. Calcd. for $C_8H_{15}O_3N$: C, 55.5; H, 8.7; N, 8.1. Found: C, 55.2; H, 8.9; N, 7.6.

The amino acid XXIb could be obtained also from the hydrochloride XXb by means of an ion exchange resin (Duolite A-2). Treatment of the amino acid XXIb with a 5% aqueous hydrochloric acid solution regenerated *cis–cis*-3-amino-2-hydroxycyclohexaneacetic acid hydrochloride (XXb).

cis–cis-Ethyl 3-amino-2-hydroxycyclohexaneacetate hydrochloride (XVIb) was obtained in poor yield when *cis–cis*-3-amino-2-hydroxycyclohexaneacetic acid (XXIb) was refluxed with ethanolic hydrogen chloride. The balance of the material was impure starting material.

***anti*-9-Hydroxy-3-oxo-2-azabicyclo[3.3.1]nonane (XVIII).** (a) **From *cis–cis*-3-Amino-2-hydroxycyclohexaneacetic Acid (XXIb).**—A suspension of *cis–cis*-3-amino-2-hydroxycyclohexaneacetic acid hydrochloride (XXb) (0.500 g.) in hot 95% ethanol (40 ml.) was treated with sodium acetate as above. The crude amino acid XXIb was heated at 240° (atmospheric pressure) for 5 minutes and sublimed at 240–245° (20 mm.) for 20 minutes. The yield of crude product was 2.87 g. (79% based on XXb), m.p. 210–230°. Two recrystallizations from ethyl acetate–ethanol afforded 2.17 g. (60%) of XVIII, m.p. 250–252° alone and mixed with previously prepared hydroxy lactam XVIII. The infrared spectra of both preparations were identical.

(b) **From *cis–cis*-Ethyl-3-Amino-2-hydroxycyclohexaneacetate Acetate (XXIIb).**—The acetate salt XXIIb (0.298 g.) was heated at 160–170° for 1.5 hr. Trituration of the product with cold ethyl acetate (3 ml.) left 0.137 g. (77%) of crude XVIII, m.p. 235–244°. One recrystallization from ethyl acetate–ethanol afforded 0.115 g. (65%) of XVIII, m.p. 251–253°.

Alternatively, the crude pyrolysis product was sublimed and then recrystallized to yield essentially the same results.

Reaction of Nitrous Acid with *cis–cis*- and *trans–cis*-Ethyl 3-Amino-2-hydroxycyclohexaneacetate (XVIb and XVa). Ethyl 2-Formylcyclopentaneacetate (XVII). (a).—A solution of *cis–cis*-ethyl-3-amino-2-hydroxycyclohexaneacetate hydrochloride (XVIb) in water (2 ml.) and acetic acid (0.5 ml.) was cooled to 0° and treated with a solution of sodium nitrite (0.298 g.) in water (2 ml.). After 3.5 hr. the excess of nitrous acid was destroyed by means of sulfamic acid and some ethanol was added to produce a homogeneous solution which was added to a warm solution containing 2,4-dinitrophenylhydrazine (0.333 g.), sulfuric acid (20 ml.) and water (330 ml.). After 10 minutes at *ca.* 80° the precipitated 2,4-dinitrophenylhydrazone was collected, washed well with water and dried *in vacuo*. The crude product (0.260 g., 57%) had m.p. 79–88° and exhibited a symmetrical maximum at 359 mμ (chloroform). The analytical sample of XVII 2,4-dinitrophenylhydrazone had m.p. 99.3–100.8° (methanol) and exhibited the same spectrum in the ultraviolet as the crude product ($\lambda_{max}^{CHCl_3}$ 359 mμ, ε 24,000).

Anal. Calcd. for $C_{16}H_{20}N_4O_6$: C, 52.7; H, 5.5; N, 15.4. Found: C, 52.3; H, 5.6; N, 15.4.

(b).—A solution of *trans–cis*-ethyl 3-amino-2-hydroxycyclohexaneacetate (XVa) (0.103 g.) in aqueous acetic acid was treated with sodium nitrite (0.125 g.) as described under (a) above. The crude 2,4-dinitrophenylhydrazone obtained (0.088 g., 47%) had m.p. 73–87° and exhibited a maximum at 360 mμ (chloroform). Chromatography of this product gave exclusively ethyl 2-formylcyclopentaneacetate 2,4-dinitrophenylhydrazone identical with the product obtained under (a) above. No evidence for the presence of ethyl 2-oxocyclohexaneacetate 2,4-dinitrophenylhydrazone could be obtained.

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