

TABLE II
YIELDS AND PROPERTIES OF RESOLVED AMINO ACIDS

Amino acid	Iso-mer	Yield, %	Concn. mg. per 2 ml.	Sol-vent	[α] _D Found, degrees	Nitrogen, %	Calcd.	Found
Aspartic acid	D ^b	63	38.3	6 N HCl	-24.7	10.5	10.4	
	L	92	40.0	6 N HCl	+25.3		10.6	
Histidine	D	55	37.5	H ₂ O	+38.5	27.1	27.1	
	L	49	33.5	H ₂ O	-38.4		27.1	
Proline	L ^a	54	32.0	H ₂ O	-84.4	12.2	12.2	
	L	47	26.8	H ₂ O	-85.1		12.1	
Serine	D	69	82.7	1 N HCl	-14.5	13.3	13.2	
	L	48	95.6	1 N HCl	+14.4		13.2	
Phenyl-alanine	D ^b	36	32.4	H ₂ O	+35.1	8.5	8.7	
	L ^b	35	31.9	H ₂ O	-34.5		8.6	
Ornithine-2 HCl	D	46	65.4	5 N HCl	-18.2 ^c	13.7	13.9	
	L	60	62.3	5 N HCl	+17.9 ^c		13.7	
Alanine	D	65	55.9	5 N HCl	-14.2	15.7	15.9	
	L ^b	61	81.7	5 N HCl	+14.2		15.8	
Methionine	D	66	52.4	6 N HCl	-22.7	9.4	9.4	
	L	54	40.0	6 N HCl	+23.6		9.4	
Valine	D ^b	52	35.5	6 N HCl	-27.3	11.9	11.9	
	L ^b	74	46.0	6 N HCl	+28.2		11.9	

^a Derived from the amide (see text). ^b Examined by the enzymatic test¹² and shown to contain less than 0.1% enantiomorph. ^c The only recorded value in 5 N HCl is $\pm 18.2^\circ$, S-C. J. Fu, K. R. Rao, S. M. Birnbaum and J. P. Greenstein, *J. Biol. Chem.*, 199, 207 (1952).

the column. After an additional several hundred ml. of water had passed through, proline amide was eluted with weak acid. In a similar non-enzymatic experiment with L-arginine and N-acetyl-DL-arginine, the acetyl derivative was eluted from the XE-64 column with water and the free amino acid removed with weak acid.

It should be pointed out that although the di-amino acids would be retained by the weak cation exchanger, XE-64, it was necessary to use the strong cation-exchange resin, Dowex-50, for the column separation in the ornithine resolution reported here. Starting with the N,N'-dichloroacetyl-amino acid, only the α -amino group is liberated. The products of the enzymatic hydrolysis are similar in their behavior on the strong exchange resin to those obtained in the resolution of the monoamino-monocarboxylic amino acids.

Results and Discussion

The results obtained with nine representative

amino acids are given in Table II. Amino acid enantiomorphs with rotation values in good agreement with those in the literature, with theoretical nitrogen analyses¹³ and, where tested with optical purity¹² of at least 99.9%, were obtained in the yields listed in Table II. These yields were calculated on the basis of the acyl or amide derivatives.

The percentage yields obtained with the small amounts employed in this study are similar to those obtained with larger amounts using the usual procedure.² A batch procedure with methionine was investigated with Dowex-50 and was considerably more complicated, involved larger volumes of solution and resulted in somewhat lower yields.

It is thus believed that, in general, the chromatographic procedure is more suitable for small amounts of material. Furthermore, in some instances, namely, proline and histidine, the column procedure is simpler than the usual technique.

The amino acids before recrystallization were, in every case tested, free of enantiomorph (better than 99.9%) when examined by the enzymatic test.¹² However, since strong HCl elution from the Dowex-50 column also carried along salts with free amino acid, the amino acid hydrochlorides obtained *directly* from the column were not *analytically* pure, as shown by low nitrogen analyses and specific rotation values one to two degrees low. The yield of both *optically* and *analytically* pure amino acid could no doubt be increased even beyond the recorded values, either by prechromatographic desalting of the enzymatic resolution mixture or by more selective elution of the free amino acid with weaker HCl at a lower amino acid load per resin column.¹⁴

(13) Analyses by R. J. Koegel and his staff.

(14) S. Moore and W. H. Stein, *Cold Spring Harbor Symposia*, 14, 179 (1949).

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Synthesis and Properties of Some 4,5,6,7-Tetrahydroisatins¹

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When 2-ketocyclohexylglyoxylic acids or esters are condensed with aromatic amines they form N-aryl-4,5,6,7-tetrahydroisatin-3-anils in excellent yields. When strongly basic amines are used in the condensation, N,N'-substituted-oxamides are isolated in addition to N-alkyl-4,5,6,7-tetrahydroisatin-3-imines. In the case of the formation of the anils it appears that the isatins are not intermediates. In the case of the imines, formed with the strongly basic amines, a possible intermediate to the symmetrically substituted oxamides is the isatin. The 3-anils and 3-imines are hydrolyzed by methanolic hydrochloric acid to the isatins. N-Substituted-4,5,6,7-tetrahydroisatins show β -keto, β -enolic, and α,β -diketo properties.

The syntheses of certain 4,5,6,7-tetrahydroindoles have been described.^{3,4} In synthetic preparations designed to prepare 4,5,6,7-tetrahydroisatins, cyclohexanone, 3- and 4-methylcyclohexanone and cyclopentanone were condensed with ethyl oxalate

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(3) (a) A. Treibs, *Ann.*, **524**, 285 (1936); (b) A. Treibs and D. Dinelli, *ibid.*, **517**, 152 (1935).

(4) A. Kötzt and L. Hesse, *ibid.*, **342**, 306 (1905).

according to the methods described by Kötzt, *et al.*⁴⁻⁶ The resulting glyoxylic acids and their esters were then treated with amines; the reaction of ethyl 4-methyl-2-ketocyclohexylglyoxylate with aniline has been described by Kötzt and Hesse.⁴

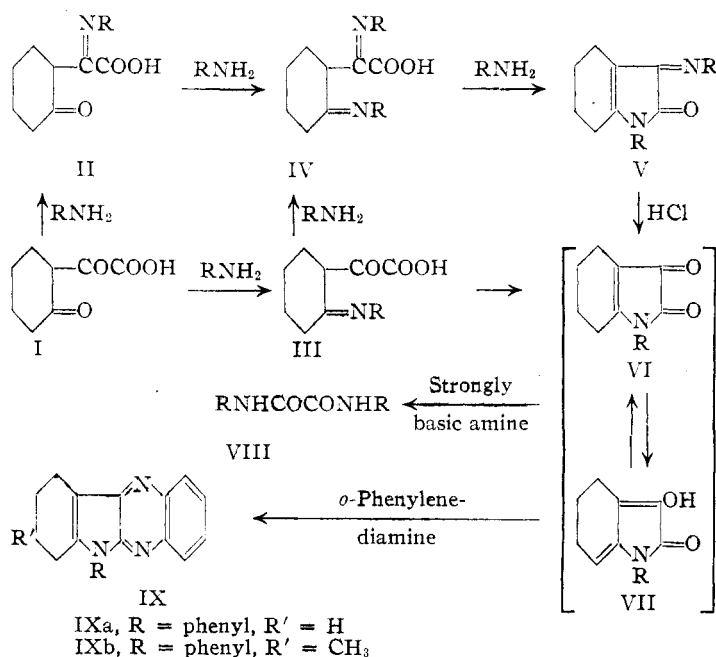
In every case where condensation products were isolated they proved to be N-substituted-4,5,6,7-tetrahydroisatin-3-anils or -3-imines. Ethyl 2-ketocyclopentylglyoxylate even under the mildest

(5) A. Kötzt, *ibid.*, **348**, 111 (1906).

(6) A. Kötzt and A. Michels, *ibid.*, **350**, 204 (1906).

conditions produced only symmetrically substituted oxamides when treated with amines.

The formation of N-substituted-4,5,6,7-tetrahydroisatin-3-anils (V) from 2-ketocyclohexylglyoxylic acids (I) can be visualized as involving initially an attack by one mole of the aromatic amine (where R indicates an aromatic group) by either of two alternative paths. The primary product would be expected to be II, rather than III, since: (a) the carbon alpha to the carboxylic acid in I should be a more positive carbon atom than the carbon atom of the ring keto group and (b) an attack by the weakly basic aromatic amine at the ring keto group could yield some III. Some formation of VI from III might be expected in that case. However, it was experimentally found that N-substituted-4,5,6,7-tetrahydroisatins did not form anils when they were treated with aromatic amines under the conditions of the condensation. In every case where an aromatic amine was used the 3-anil derivative was isolated in excellent yield from either the 2-ketocyclohexylglyoxylic acid or its ethyl ester. In either event II or III could react with another mole of aromatic amine to form IV. In turn IV can form V.



When strongly basic amines (where R indicates an alkyl group) were condensed with 2-ketocyclohexylglyoxylic acids or esters, N,N'-substituted-oxamides (VIII) were isolated in addition to N-substituted-4,5,6,7-tetrahydroisatin-3-imines (V). The formation of oxalic acid or its salts from various 2-ketoglyoxylic acids is known to occur under the influence of acids and bases.⁷ In the case of 2-ketoglyoxylic esters amines produce N,N'-substituted-oxamides.⁷ One possible interpretation of the formation of the amide VIII from 2-ketocyclohexylglyoxylic acids lies in the fact that strongly basic amines are more likely to attack both keto groups in I to form II and III simul-

taneously. Some of III could then form the isatin VI. By acid hydrolysis of the anil (V), VI was isolated and shown to form symmetrically substituted oxamides (VIII) in 70% yields when treated with strongly basic amines under the conditions of the condensation.

Evidence as to the rupture of the cyclic amide can be shown by the fact that when N-phenyl-4,5,6,7-tetrahydroisatin was treated with benzylamine, N,N'-dibenzylloxamide was isolated. N-Phenyl-N'-benzylloxamide was recovered unchanged by treatment with benzylamine under the same conditions.

Acid hydrolyses of the N-substituted-4,5,6,7-tetrahydroisatin-3-anils or -3-imines produced N-substituted-4,5,6,7-tetrahydroisatins. These appear to exist in an equilibrium corresponding to structures VI and VII. When ferric chloride was added to a methanolic solution of these isatins an immediate dark greenish coloration was produced. These isatins were soluble in cold 10% sodium hydroxide solution and did not form anils with aniline under the conditions of the condensation reaction. The β -enol structure VII is indicated also by the formation of the 3-methyl ether of the enol form of the N-phenyl-4,5,6,7-tetrahydroisatin.⁸ The β -keto form VI is shown by the isolation of the 3-phenylhydrazone of the above isatin. Further, with *o*-phenylenediamine, quinoxaline derivatives (IX) were isolated. These reactions are best interpreted in terms of a tautomeric equilibrium involving structures VI and VII.

When the various 2-ketocyclohexylglyoxylic acids were treated with ammonium hydroxide in the cold only oxamide was isolated. When dry ammonia was bubbled into a chilled ethanolic solution of the various 2-ketocyclohexylglyoxylic acids or ethyl esters a white precipitate formed in each case. The crystals which were collected emitted ammonia fumes on standing; finally oxamide was isolated.

When cyclohexanone was condensed with ethyl oxamate, 2,6(or 2,2)-diglyoxal-amidecyclohexanone was isolated. The condensation of 3-methyl-cyclohexanone with ethyl oxamate probably yielded 4-methyl-2-ketocyclohexylglyoxalamide. However, attempts to hydrolyze this product to the known 4-methyl-2-ketocyclohexylglyoxylic acid yielded oxamic acid even under the mildest conditions.

Experimental⁹

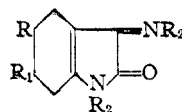
Formation of the Various 2-Ketocyclohexylglyoxylic Esters and Acids. (a).—2-Ketocyclohexylglyoxylic acid and its ethyl ester, 4-methyl-2-ketocyclohexylglyoxylic acid and its ethyl ester⁴ and ethyl 2-ketocyclopentylglyoxylate⁵ were prepared by condensing ethyl oxalate with the appropriate ketones. The yield of the latter ester was improved somewhat by effecting the condensation at -10° .

(8) For the similar reactions of the unsaturated lactones formed by the glyoxylation of 2-arylcyclohexanones see W. E. Bachmann, G. I. Fujimoto and L. B. Wick, *THIS JOURNAL*, **72**, 1995 (1950).

(9) All m.p.s are uncorrected; microanalyses by W. Manser, Zürich, Switzerland.

(7) O. Mumm and C. Bergell, *Ber.*, **45**, 3040 (1912).

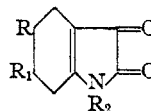
TABLE I

N-SUBSTITUTED-4,5,6,7-TETRAHYDROISATIN-3-IMINES,^a

R	R ₁	R ₂	Pro- cedure	Form	M.p., °C.	Yield, %	Empirical formula	Carbon, % Calcd. Found	Hydrogen, % Calcd. Found	Nitrogen, % Calcd. Found
H	H	C ₆ H ₅	A ^b	Yellow prisms	192-193	95	C ₂₂ H ₁₅ N ₂ O	79.44 79.45	5.96 5.99	9.27 9.30
H	H	<i>p</i> -CH ₃ C ₆ H ₄	A ^b	Greenish-yellow prisms	203-204	95	C ₂₂ H ₁₅ N ₂ O	80.00 80.14	6.67 6.81	8.49 8.44
H	H	<i>o</i> -CH ₃ C ₆ H ₄	A ^b	White needles	126-127	90	C ₂₂ H ₁₅ N ₂ O	80.00 79.77	6.67 6.66	8.49 8.60
H	H	2-C ₁₀ H ₇	A ^b	White prisms	264-265	87	C ₂₂ H ₁₅ N ₂ O			6.97 6.97
H	H	(CH ₃) ₂ CHCH ₂	B ^b	White needles	69-69.5	10	C ₁₆ H ₁₁ N ₂ O			10.69 10.79
H	H	C ₆ H ₅ CH ₂	B ^b	White needles	91-91.5	59	C ₂₂ H ₁₅ N ₂ O	80.00 79.82	6.67 6.73	8.49 8.30
H	CH ₃	C ₆ H ₅	A ^c	Green needles	162-162.5	80	C ₂₁ H ₁₃ N ₂ O			8.86 8.80
H	CH ₃	<i>p</i> -CH ₃ C ₆ H ₄	A ^c	Green prisms	174-175	90	C ₂₁ H ₁₃ N ₂ O	80.23 80.09	6.98 6.82	8.14 8.09
H	CH ₃	C ₆ H ₅ CH ₂	B ^c	Yellow needles	99-100	24	C ₂₁ H ₁₃ N ₂ O	80.23 80.31	6.98 6.70	8.14 8.20
CH ₃	H	<i>p</i> -CH ₃ C ₆ H ₄	A ^d	Yellow plates	183-183.5	..	C ₂₁ H ₁₃ N ₂ O	80.23 80.40	6.98 7.15	8.14 8.03

^a All compounds were recrystallized from methanol. ^b Prepared equally well from 2-ketocyclohexylglyoxylic acid or its ethyl ester in essentially equivalent yields of crude product. ^c Yields are those obtained from 4-methyl-2-ketocyclohexylglyoxylic acid. The undistilled ester gave the same product. ^d Undistilled ethyl 5-methyl-2-ketocyclohexylglyoxylate was used in this preparation.

TABLE II

N-SUBSTITUTED-4,5,6,7-TETRAHYDROISATINS,^a

R	R ₁	R ₂	Form	M.p., °C.	Yield, %	Empirical formula	Carbon, % Calcd. Found	Hydrogen, % Calcd. Found	Nitrogen, % Calcd. Found
H	H	C ₆ H ₅	Yellow prisms	183-184	93	C ₁₄ H ₁₁ NO ₂	74.01 73.83	5.73 5.86	6.17 6.31
H	H	<i>p</i> -CH ₃ C ₆ H ₄	Yellow prisms	193-194	68	C ₁₅ H ₁₁ NO ₂	74.69 74.47	6.22 6.20	5.81 5.89
H	H	<i>o</i> -CH ₃ C ₆ H ₄	White needles	183-184	72	C ₁₅ H ₁₁ NO ₂	74.69 74.32	6.22 6.22	5.81 5.93
H	H	C ₆ H ₅ CH ₂	White needles	163-164	95	C ₁₅ H ₁₁ NO ₂	74.69 74.86	6.22 6.31	5.81 5.90
H	CH ₃	C ₆ H ₅	Yellow needles	165-166	84	C ₁₄ H ₁₁ NO ₂			5.81 5.67
H	CH ₃	<i>p</i> -CH ₃ C ₆ H ₄	White prisms	181-182	64	C ₁₅ H ₁₁ NO ₂			5.49 5.30
CH ₃	H	<i>p</i> -CH ₃ C ₆ H ₄	White plates	192-193	30	C ₁₆ H ₁₇ NO ₂	75.29 75.04	6.67 6.66	5.49 5.29

^a Prepared by procedure C. All products were recrystallized from methanol. These isatins are soluble in cold 10% sodium hydroxide solution and give an immediate deep green or blackish color in alcoholic solution upon the addition of ferric chloride.

(b).—Ethyl 5-methyl-2-ketocyclohexylglyoxylate was prepared by adding a solution formed from the reaction of 4.6 g. (0.2 mole) of sodium with 85 ml. of absolute ethanol to a chilled solution of 22.4 g. (0.2 mole) of 4-methylcyclohexanone and 29.6 g. (0.2 mole) of ethyl oxalate. During the addition the temperature was not allowed to rise over 10°, and the resulting solution was then allowed to stand overnight. The solution was then diluted with water and acidified with dilute hydrochloric acid in the cold; an oil separated to the bottom of the flask. This oil, when isolated and dried, was difficult to distill due to loss of carbon monoxide. When the condensation product was acidified and steam distilled no 5-methyl-2-ketocyclohexylglyoxylic acid was isolated.

Therefore, the alcoholic solution of the sodium salt was diluted with water and extracted with ether until the ether extracts were no longer colored. The aqueous layer was then cautiously acidified and extracted with ether until the ether extracts were no longer colored. These ether extracts were dried over anhydrous sodium sulfate. This dried straw-colored solution was used in subsequent reactions.

N-Phenyl-4,5,6,7-tetrahydroisatin-3-anil. Procedure A.—A typical example is as follows: A mixture of 2.0 g. of 2-ketocyclohexylglyoxylic acid, 4.0 g. of aniline and 10 ml. of methanol was heated with constant stirring on the steam-bath for two hours. Upon cooling, the entire mixture solidified. The material was filtered and washed with the aid of cold methanol and then dried; yield 95-100% of crude product, m.p. 190-193°. Recrystallizations from methanol furnished shiny yellow prisms; m.p. 192-193°. Ethyl 2-ketocyclohexylglyoxylate was used with equivalent results.

N-Benzyl-4,5,6,7-tetrahydroisatin-3-benzylimine. Procedure B.—This procedure was used for condensations with strongly basic amines. To a chilled solution of 1.0 g. of 2-ketocyclohexylglyoxylic acid in 12 ml. of methanol was added 4 ml. of benzylamine. After allowing to cool to

room temperature the mixture was heated on the steam-bath for three hours and filtered while hot. The white platelets of N,N'-dibenzylloxamide, after washing with methanol and air drying, weighed 0.3 g., m.p. 215-216°. The melting point was not depressed when mixed with an authentic sample. Upon cooling the hot filtrate, the imine separated and was obtained as white crystals after recrystallization from methanol; yield 1.0 g., m.p. 91-91.5°.

N-Phenyl-4,5,6,7-tetrahydroisatin. Procedure C.—A suspension of 5.5 g. of N-phenyl-4,5,6,7-tetrahydroisatin-3-anil in 40 ml. of isopropyl alcohol and 25 ml. of concentrated hydrochloric acid was refluxed for two hours. At the end of this time a light red solution was obtained. The solution was filtered and concentrated. Upon cooling, the yellow prisms which separated were collected and washed well with water; yield 3.8 g. (95%), m.p. 183-184°. Recrystallizations from methanol did not change the melting point. Good yields of pure material could also be obtained by drowning the solution in excess water and filtering.

The isatin gave an immediate deep-greenish color in alcoholic solution with ferric chloride. It was soluble in cold 10% sodium hydroxide solution.

The 3-enol methyl ether was formed by adding an ethereal solution of diazomethane to a solution of N-phenyl-4,5,6,7-tetrahydroisatin (0.25 g.) in acetone at 0°. The mixture was kept at 0° for several hours and then allowed to evaporate to dryness at room temperature. To the oily residue was added 2 ml. of methanol and the crystals which formed were collected; yield 0.2 g. By recrystallization from methanol the enol ether was obtained as yellow needles; m.p. 83-84°. The ether is insoluble in alkali and gives no color with ferric chloride.

Anal. Calcd. for C₁₅H₁₁NO₂: C, 74.69; H, 6.22; N, 5.81. Found: C, 74.83; H, 6.57; N, 5.69.

The 3-phenylhydrazone, prepared in acetic acid, crystallized from ethanol as pale yellow needles, m.p. 244°.

The phenylhydrazone is insoluble in alkali and gives no color with alcoholic ferric chloride.

Anal. Calcd. for $C_{20}H_{19}N_3O$: C, 75.71; H, 5.99; N, 13.25. Found: C, 75.96; H, 6.02; N, 13.02.

When excess aniline was added to an alcoholic solution of the isatin and the mixture heated on the steam-bath for several days, the unreacted isatin was quantitatively recovered.

When benzylamine was added to a methanolic solution of N-benzyl- or N-phenyl-4,5,6,7-tetrahydroisatin and the resulting mixture heated on the steam-bath for several hours a white precipitate gradually appeared. Upon cooling and filtering a 70% yield of N,N'-dibenzylloxamide was obtained in each case; m.p. 215° alone and mixed with authentic specimens. With isobutylamine, 70% yields of N,N'-diisobutylloxamide were obtained with both of these isatins; m.p. 166.5–167° alone and when mixed with separately synthesized specimens.

When N-phenyl-N'-benzylloxamide was treated with benzylamine in methanol under similar conditions it was recovered quantitatively.

Preparation of the Quinoxaline Derivatives. (a) 6-Phenyl-7,8,9,10-tetrahydro-indolo[2,3-b]quinoxaline (IXa).—A mixture of 1.6 g. of N-phenyl-4,5,6,7-tetrahydroisatin, 0.9 g. of *o*-phenylenediamine, 8 ml. of water and 3 ml. of glacial acetic acid was refluxed for two hours. After cooling, the upper layer was decanted from the brown oil which was washed with water and then dissolved in hot methanol. From the cooled solution 0.5 g. (24%) of yellow crystals deposited. The quinoxaline crystallized from methanol in yellow prisms, m.p. 159–160°.

Anal. Calcd. for $C_{20}H_{17}N_3$: C, 80.27; H, 5.69; N, 14.05. Found: C, 79.94; H, 5.88; N, 14.27.

(b) 6-Phenyl-8-methyl-7,8,9,10-tetrahydro-indolo[2,3-b]-quinoxaline (IXb).—From 1.5 g. of N-phenyl-6-methyl-4,5,6,7-tetrahydroisatin, 1.0 g. of *o*-phenylenediamine, 4 ml. of glacial acetic acid and 10 ml. of water, 0.3 g. (15%) was obtained by the procedure described above. The

quinoxaline crystallized from methanol as yellow needles, m.p. 199–200°.

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80.51; H, 6.07; N, 13.42. Found: C, 80.55; H, 6.19; N, 13.50.

2,6(or 2,2)-Diglyoxalamidecyclohexanone.—A solution prepared from 2.3 g. of sodium and 50 ml. of absolute ethanol was added with stirring to a mixture of 9.8 g. of cyclohexanone and 11.7 g. of ethyl oxamate cooled to below 10°. The resulting suspension was stirred for several hours and then allowed to stand overnight. The mixture was diluted with 100 ml. of water and neutralized with dilute hydrochloric acid in the cold. The solid product which separated was collected and recrystallized from acetone; yield 6.0 g., m.p. 185–186° (foaming). The product produced no coloration with ferric chloride solution and was cleaved readily to oxamic acid by acid or base.

Anal. Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.00; N, 11.67. Found: C, 50.02; H, 4.98; N, 11.77.

4(or 6)-Methyl-2-ketocyclohexylglyoxalamide.—A solution prepared from 2.3 g. of sodium and 50 ml. of anhydrous ethanol was added with stirring to a mixture of 11.2 g. of 3-methylcyclohexanone and 11.7 g. of ethyl oxamate. During the addition the temperature was kept below 10°. Stirring was continued until the contents of the flask reached room temperature and then it was allowed to stand overnight. The mixture was diluted with 50 ml. of water and made neutral by the addition of dilute hydrochloric acid in the cold. The white solid which formed was collected and recrystallized from methanol; yield 6.9 g., m.p. 147–148°. The glyoxalamide showed no color reaction with ferric chloride and attempts to hydrolyze to the known 4-methyl-2-ketocyclohexylglyoxylic acid produced only oxamic acid.

Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.01; H, 7.10; N, 7.65. Found: C, 58.98; H, 7.00; N, 7.58.

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Dipole Moments and Conformations of Androstane-3,17-dione and of Etiocholine-3,17-dione

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The dipole moments of androstane-3,17-dione and of etiocholine-3,17-dione, derived from dielectric constant measurements of benzene solutions of these substances are 3.1 and 3.5 *D*, respectively. Assuming an "all chair" conformation of the A/B/C ring system in each derivative, the dipole moments of the two compounds should be identical, and equal to 3.04 *D*. The discrepancy between the observed and calculated values for etiocholine-3,17-dione suggests the presence, at equilibrium, of about 16% of the ring A "boat" form, which possesses a dipole moment of 5.28 *D*.

The greater thermodynamic stability of the "chair" conformation of cyclohexane with respect to the "boat" modification is well known and is supported by several independent lines of evidence. Pertinent to the present discussion are dipole moment measurements of Le Fèvre and Le Fèvre¹ for cyclohexane-1,4-dione. The moments calculated for the "chair" and "boat" forms of this substance are, respectively, zero and 4.1 *D*, as compared with an experimentally determined value (benzene solution) of 1.2 *D*. Simple calculations employing the squares of the dipole moments indicate that in solution the "chair" form predominates to the extent of about 91% at equilibrium.¹ The energy difference between the "chair" and "boat" conformations of cyclohexane in the gas phase (25°)

has been estimated by Beckett, Pitzer and Spitzer² to be of the order of 5.6 kcal. in favor of the more stable "chair" structure.

Information regarding fused ring systems, although not as extensive as that for cyclohexane and its derivatives, is in general agreement with the idea that "chair" structures are more stable than the corresponding "boat" conformations. Detailed X-ray analyses of cholesteryl iodide, 3β,5α-dichlorocholestane, and related products³ support this conclusion. An important contribution to the structural theory of fused rings is the demonstration of Bastiansen and Hassel,⁴ based upon electron diffraction studies, that *cis*-decalin possesses the

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

(3) D. Crowfoot, "Vitamins and Hormones," R. S. Harris and K. V. Thimann, Vol. II, Academic Press, Inc., New York, N. Y., 1949, p. 409.

(4) O. Bastiansen and O. Hassel, *Nature*, **157**, 765 (1946).

(1) C. G. Le Fèvre and R. J. W. Le Fèvre, *J. Chem. Soc.*, 1696 (1935).