[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Kolbe Electrolyses[1] of Perhydrodiphenic Acids

BY C. G. OVERBERGER AND PETER KABASAKALIAN[2]

RECEIVED JANUARY 7, 1957

The Kolbe electrolysis of *cis–syn–cis-*, *trans–anti–trans-* and *trans–syn–trans*-perhydrodiphenic acids in anhydrous methanol is described. In all cases, the principal product was a γ-lactone. The structure of the γ-lactone was established by chemical synthesis. The formation of the γ-lactone may involve a hydrogen radical transfer reaction.

The electrolysis of dibasic acids (from malonic to sebacic) in aqueous media have been reported[3] to yield olefins and alcohols, containing two carbons less than the starting material. The structures of the olefins and the alcohols obtained were both the expected ones as well as their isomers. The latter may have been formed by migration of hydrogen atoms in the originally formed radicals.

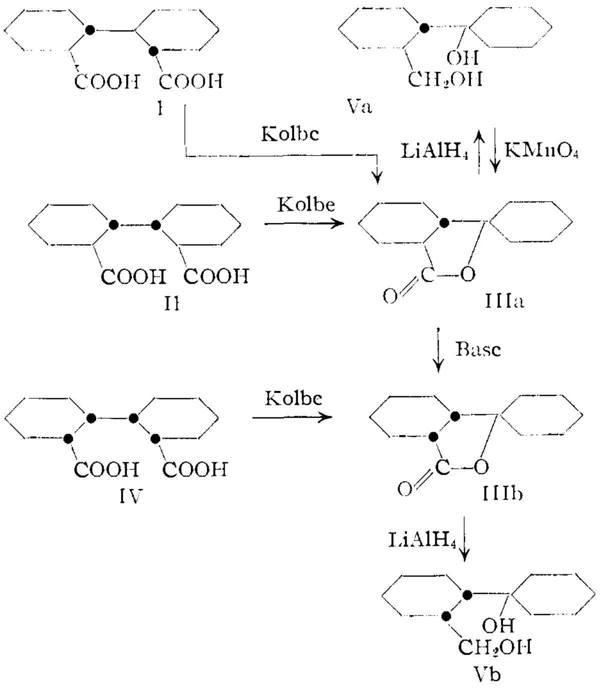
Although all attempts to isolate the coupled product, cycloalkanes, have not been successful, Vanzetti[3d] has reported the formation of a small amount of lactone during the electrolysis of suberic acid. This paper describes an initial phase of the study of Kolbe electrolyses of dibasic acids in anhydrous methanol.

The Kolbe electrolysis products from the perhydrodiphenic acids were separated into a steam-distillable fraction (monomeric) and a non-steam-distillable fraction (polymeric). The non-steam-distillable fractions account for about 20–25% of the product and were presumed to be made up of polymeric material. The steam-distillable fractions, which account for about 60% of the product, contain about 20% of non-lactonic material which was not identified.

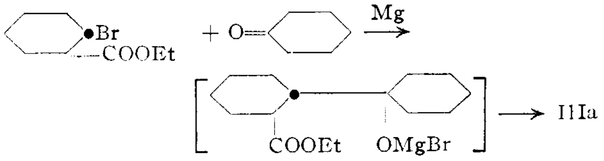
The Kolbe electrolysis of the three perhydrodiphenic acids studied here gave as a minor product (about 5%) δ-lactones. These probably were formed by the intramolecular coupling of the primary and the secondary radicals formed at the anode and were identified only by their infrared spectrum. Their infrared absorption band at 5.76 μ is indicative of a saturated six-membered lactone, but an open chain ester[4] cannot be excluded.

The electrolysis of *trans–anti–trans* (I) and *trans–syn–trans* (II) perhydrodiphenic acids gave as the major product (about 45%) the *trans*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid (IIIa), while the electrolysis of *cis–syn–cis* (IV) perhydrodiphenic acid gave the *cis*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid (IIIb). These isomeric γ-lactones from the Kolbe electrolyses could not be obtained stereochemically pure since isomerization conditions prevailed during their preparation.

The structure of the *trans*-γ-lactone was verified in the following way. Reduction with lithium aluminum hydride gave the *trans*-glycol (90%). This product was found to have only one hydroxyl group which could be acetylated easily. The *trans*-γ-lactone (37%) was regenerated when the *trans*-glycol was oxidized with alkaline potassium permanganate.



The *cis*- and *trans*-γ-lactones were synthesized by independent routes for reference purposes. The *trans* isomer was prepared from the ethyl ester of *trans*-2-bromocyclohexanecarboxylic acid in low yield by means of the Grignard reaction with cyclohexanone as indicated.



The cylization of the initial Grignard product of this type also has been reported by Cason, Adams, Bennett and Register[5] who prepared γ-substituted γ-lactones by the action of Grignard reagents on levulinic esters.

The *cis* isomer was prepared by two methods. The first method[6] involved a Diels–Alder reaction

---

[1] For the previous paper, see C. G. Overberger and P. Kabasakalian, *J. Org. Chem.*, **21**, 1124 (1956).

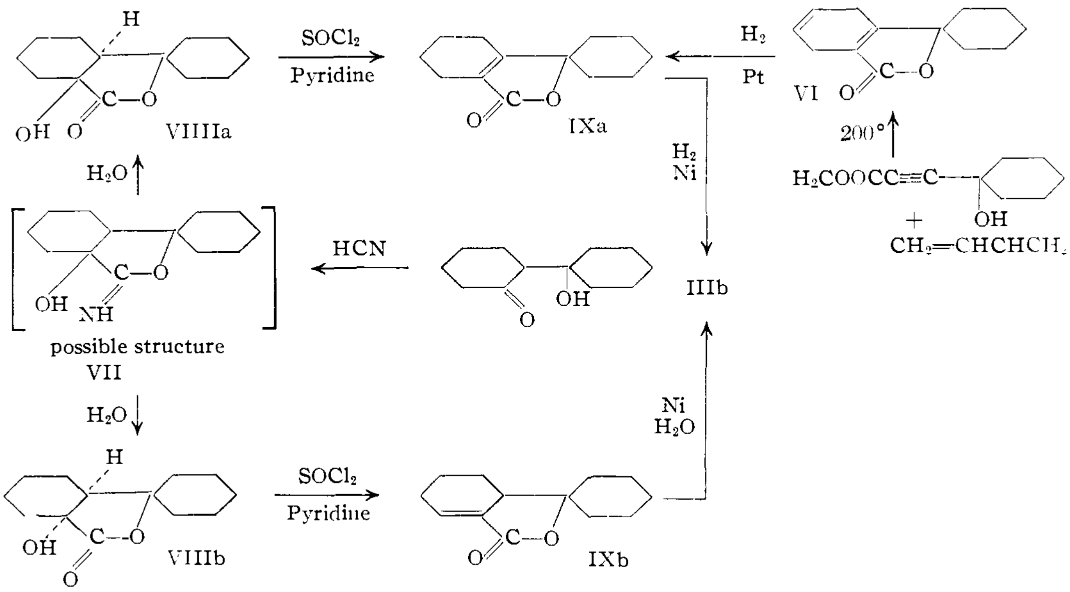
[2] This paper comprises a portion of a thesis presented by Peter Kabasakalian in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of the Polytechnic Institute of Brooklyn.

[3] (a) B. L. Vanzetti, *Gazz. chim. ital.*, **34**, II, 511 (1904); (b) B. L. Vanzetti, *ibid.*, **37**, II, 340 (1907); (c) B. L. Vanzetti, *ibid.*, **38**, I, 47 (1908); (d) B. L. Vanzetti, *ibid.*, 390 (1907).

[4] R. S. Rasmussen and R. R. Brattain, THIS JOURNAL, **71**, 1073 (1949).

[5] J. Cason, C. E. Adams, L. L. Bennett, Jr., and U. D. Register' *ibid.*, **66**, 1764 (1944).

[6] We are indebted to Mr. John Whelan for the initial suggestion.



between butadiene and the methyl ester of β-(1-hydroxycyclohexyl)-propiolic acid to give the lactone of 2-(1-hydroxycyclohexyl)-1,4-cyclohexadiene-1-carboxylic acid (68%). Catalytic reduction with the aid of Adams catalyst eliminated the isolated double bond to form the lactone of 2-(1-hydroxycyclohexyl)-1-cyclohexene-1-carboxylic acid (89%). Further reduction with the aid of Raney nickel and high pressure yielded the *cis*-γ-lactone (82%).

The second method for the preparation of the *cis* isomer used 2-(1-hydroxycyclohexyl)-cyclohexanone as starting material. Two methods are reported for the preparation of this compound and different melting points are recorded. Colonge's[7] method involved treating cyclohexanone with the reaction product from methyl Grignard reagent and N-methylaniline (m.p. 56°). Stanek's[8] method involved the self-condensation of cyclohexanone with ethanolic potassium hydroxide as the basic catalyst (m.p. 160°). The first step in this route involved the formation of cyanohydrins, which immediately cyclized to form probably five-membered cyclic imidic acid esters. These were not purified and on hydrolysis gave hydroxy-γ-lactones. Although Stanek's β-ketol gave a hydroxy-γ-lactone, the carbon and hydrogen analyses of the β-ketol and the hydroxy-γ-lactone were not in agreement with the proposed structure.

Colonge's β-ketol gave two isomeric hydroxy-γ-lactones (89%). One was a solid which is presumed to be the *trans* form from the stereochemistry of the subsequent dehydration step. It accounted for 20% of the total hydroxy lactone. The major fraction was a liquid and is presumed to be the *cis* form from the stereochemistry of the following dehydration step.

Parham, Moulton and Zuckerbraun[9] have reported that the dehydration of 2-phenylcyclohexanone cyanohydrin with thionyl chloride in pyridine is kinetically controlled, resulting in the *trans* elimination of the hydroxyl group. Using the same reaction conditions, thionyl chloride in pyridine, each of the isomeric hydroxy-γ-lactones was dehydrated and found to yield a different unsaturated lactone. The *trans* isomer gave the $\Delta^{1,2}$-product (90%) while the *cis* isomer gave the $\Delta^{1,6}$-product (72%). High pressure reduction, using Raney nickel catalyst, of the $\Delta^{1,6}$-unsaturated lactone also gave the *cis*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid (75%). The *cis*-γ-lactone was reduced with lithium aluminum hydride to give the *cis*-glycol (98%).

Both the *cis*- and *trans*-γ-lactones were isomerized separately with sodium methoxide in anhydrous methanol. Identical equilibrium mixtures were obtained from both; the equilibrium mixture from the *cis* isomer was found to contain 90% *cis*- and 10% *trans*-γ-lactone while the equilibrium mixture from the *trans* isomer was found to contain 91% *cis*- and 9% *trans*-γ-lactone. Thus, the *cis* isomer seemed to be the most stable one at equilibrium.

The melting points of various pairs of isomers obtained in this study are listed in Table I.

TABLE I

ISOMERIC PAIRS

Compound	Isomer	M.p., °C.
Lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid	*cis* *trans*	55–56 99–99.5
2-(1-Hydroxycyclohexyl)-cyclohexane-methanol	*cis* *trans*	117–118 92.5–93
Lactone of 2-(1-hydroxycyclohexyl)-1-hydroxycyclohexanecarboxylic acid	*cis* *trans*	? 159–161
Lactone of 2-(1-hydroxycyclohexyl)-cyclohexene-1-carboxylic acid	$\Delta^{1,2}$ $\Delta^{1,2}$	79–80 71–72

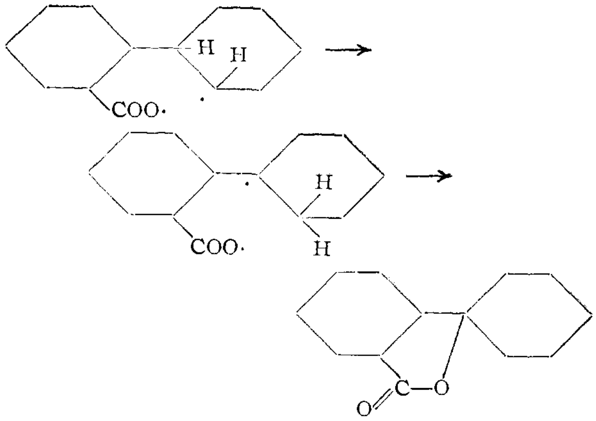
A possible mechanism for the formation of the γ-lactones may involve a hydrogen radical transfer at the location of the secondary radical, followed by an intramolecular coupling of the rearranged radical and the primary radical formed at the anode.

---

(7) J. Colonge, *Bull. soc. chim. France*, [5] **1**, 1101 (1934).

(8) J. Stanek, *Chem. Listy*, **46**, 110 (1952).

(9) W. E. Parham, W. N. Moulton and A. Zuckerbraun, *J. Org. Chem.*, **21**, 72 (1956).



Urry[10] and Muhs,[11] who studied the alcoholic electrolyses of monocarboxylic acids which generated radical intermediates containing a quaternary carbon adjacent to a primary carbon that was the original radical site, found that of the products formed only those from a single radical showed rearrangement. The products formed from two radicals (coupled and ester products) were unrearranged.

The possibility of other mechanisms to explain the five-membered lactone cannot be excluded. Thus, lactonization could have occurred by ionic processes involving addition of a radical or an ion derived from one carboxyl group to an olefin linkage in the adjacent ring formed from radical disproportionation. The possibility that hydrogen migration occurred by an ionic transfer to a carbonium ion formed by oxidation of the radical at the anode also cannot be discounted completely until further evidence is obtained.

Acknowledgment.—We wish to thank the Schering Corporation for the generous use of their laboratory facilities in this work.

Experimental[12]

Absorption Spectra.—The ultraviolet absorption spectra were measured in 1-cm. quartz cells in methanol solutions using a Cary model 11 recording spectrophotometer. Infrared absorption spectra were obtained with a Perkin-Elmer model 21 double beam recording spectrophotometer with a sodium chloride prism.

Electrolyses.—The electrolysis equipment, conditions and electrode preparation were identical to those reported by Overberger and Kabasakalian.[1]

Kolbe Electrolysis of *trans–syn–trans*-Perhydrodiphenic Acid[13] (II).—A solution of 1.7 g. (0.050 mole) of II in 60 ml. of anhydrous methanol and 10 ml. of 0.20 *N* sodium methoxide was electrolyzed. The electrolysis required about 6 hr. (the current continually decreased and the anode became coated with insoluble material). The electrolyzed solution which was almost neutral was distilled under atmospheric pressure until the distillation temperature started to rise above 70° and most of the methanol was removed. The reaction mixture was then subjected to steam distillation; 6.0 l. of distillate was collected and extracted with ether. The extracts were dried over calcium chloride and concentrated to give 6.46 g. of liquid, fraction A, from which 0.63 g. of solids crystallized, m.p. 87–90°. This sample contained a small amount of the isomeric γ-lactone which could not be separated. Most of fraction A is a mixture of the isomeric γ-lactones (see later Experimental). The infrared spectrum of this solid in a Nujol mull indicated a γ-lactone.[4] Subsequently, this spectrum was found to be identical with the spectrum of the *trans*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid (IIIa).

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; mol. wt., 208. Found: C, 75.04; H, 9.62; mol. wt., 213 (cryoscopic).

The non-steam-distillables amounted to 1.95 g. The infrared spectrum of fraction A in carbon disulfide indicated approximately 70% γ-lactone[4] and 10% δ-lactone.[4]

Kolbe Electrolysis of *trans–anti–trans*-Perhydrodiphenic Acid[13] (I).—A solution of 1.27 g. (0.0050 mole) of I in 70 ml. of anhydrous methanol and 1 ml. of 0.20 *N* sodium methoxide was electrolyzed. The electrolyzed solution was treated as described above to give 0.605 g. of liquid, fraction A, from which 0.138 g. of solid crystallized, m.p. 84–86°. This sample contained a small amount of the isomeric γ-lactone which could not be separated. Most of fraction A is a mixture of the isomeric γ-lactones. The infrared spectrum of this solid in a Nujol mull was identical with the spectrum of the *trans*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid (IIIa). It was not possible to remove all traces of the *cis*-lactone in this synthetic product also (see later Experimental).

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.78; H, 9.64.

Fraction B, the non-steam-distillables, amounted to 0.197 g. The infrared spectrum of fraction A in carbon disulfide indicated approximately 70% γ-lactone and 10% δ-lactone.

Kolbe Electrolysis of *cis–syn–cis*-Perhydrodiphenic Acid[13] (IV).—A solution of 1.27 g. (0.0050 mole) of IV in 70 ml. of anhydrous methanol and 5 ml. of 0.20 *N* sodium methoxide was electrolyzed. The electrolyzed solution was treated as described above to give 0.479 g. of liquid, fraction A, from which 0.1 g. of solid crystallized, m.p. 48–52°. This sample contained a small amount of the isomeric γ-lactone which could not be separated. Most of fraction A is a mixture of the isomeric γ-lactones. The infrared spectrum in Nujol mull was identical with the spectrum of the *cis*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid (IIIb).

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.14; H, 9.68.

Fraction B, the non-steam-distillables, amounted to 0.139 g. The infrared spectrum of fraction A in carbon disulfide indicated approximately 70% γ-lactone and 10% δ-lactone.

Preparation of *trans*-2-(1-Hydroxycyclohexyl)-cyclohexanemethanol (Va).—To 0.40 g. (0.10 mole) of lithium aluminum hydride suspended in 50 ml. of anhydrous ether, a solution of 1.00 g. (0.0048 mole) of IIIa, from the Kolbe electrolysis, in 50 ml. of ether, was added dropwise according to the general procedure of Nystrom and Brown.[14] The mixture was refluxed for 1 hr., cooled and 10% sodium hydroxide was added. The ether was decanted and the precipitate which had formed was triturated with more ether. The combined ether extracts were dried over calcium chloride and concentrated to give 0.918 g. (90%) of the glycol. Recrystallization from pentane yielded a solid, m.p. 92.5–93°.

Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39; primary OH equiv., 212. Found: C, 73.40; H, 11.32; primary OH equiv., 233.[15]

The infrared spectrum of a Nujol mull indicated the OH frequency.[16] The quantitative determination of total primary and secondary hydroxyls was made according to the method of Ogg, Porter and Willits.[15]

Oxidation of *trans*-2-(1-Hydroxycyclohexyl)-cyclohexanemethanol (Va).—To a mixture of 0.100 g. (0.00047 mole) of Va, 0.150 g. of potassium hydroxide and 7.5 ml. of water, was added 5 ml. of aqueous potassium permanganate (1:15) according to the general procedure of Billman and Parker.[17]

---

[10] W. H. Urry, Abstracts of the Twelfth National Organic Chemistry Symposium of the American Chemical Society, Denver, Colo., 1951, p. 36.

[11] M. A. Muhs, Ph.D. Thesis, University of Washington, Seattle, Washington, 1954.

[12] All melting points are corrected.

[13] R. P. Linstead and W. E. Doering, This Journal, **64**, 1991 (1942).

[14] R. F. Nystrom and W. G. Brown, *ibid.*, **69**, 1197 (1947); **69**, 2548 (1947).

[15] C. L. Ogg, W. L. Porter and C. O. Willits, *Ind. Eng. Chem., Anal. Ed.*, **17**, 394 (1945).

[16] W. Weniger, *J. Opt. Soc. Amer.*, **7**, 517 (1923); *Phys. Rev.*, **31**, 388 (1910).

[17] J. H. Billman and E. E. Parker, This Journal, **65**, 2455 (1943).

The mixture was stirred for 1 hr. and then filtered. Sodium bisulfite was added to the filtrate to remove unreacted potassium permanganate and then the solution was acidified. A cloudy solution was otbained which was placed in the refrigerator. Crystals grew which were filtered and washed with water to give 0.036 g. (37%), 99–99.5°.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.97; H, 9.45.

The infrared spectrum in a Nujol mull indicated a γ-lactone. The spectrum was identical to the spectrum of IIIa.

Preparation of the *trans*-Lactone of 2-(1-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid (IIIa).—To a mixture containing 16 g. (0.67 g. atom) of magnesium turnings, 0.5 g. of mercuric chloride and 100 ml. of dry tetrahydrofuran, was added a solution of 94 g. (0.40 mole) of the ethyl ester of *trans*-2-bromocyclohexanecarboxylic acid[18] and 40 g. (0.41 mole) of cyclohexanone in 100 ml. of tetrahydrofuran according to the general procedure of Miller and Nord.[19] The mixture was refluxed overnight on a steam-bath. After stopping the reaction by addition of dilute hydrochloric acid, the reaction solution was extracted with ether. The ether layer was washed with water, aqueous sodium bicarbonate and water again, dried over calcium chloride and concentrated to an oil. The infrared spectrum of a film showed a small amount of γ-lactone. The oil was saponified with 25% potassium hydroxide solution according to the procedure of Miller and Nord.[19] The basic solution was extracted with ether, then acidified and extracted again. The ether extract of the acid solution was dried over calcium chloride and concentrated to a residue. The infrared spectrum of this acid fraction indicated a small amount of γ-lactone. With the aid of a *p*H meter, this acid, dissolved in methanol, was titrated to an equivalence point with aqueous sodium hydroxide. After the addition of water, the solution was extracted with ether and the extract concentrated to an oil. Steam distillation of this oil gave 3.809 g. (4.6%) of the γ-lactone from which 0.740 g. of solid crystallized, m.p. 86–91°. This sample contained a small amount of the isomeric γ-lactone which could not be separated.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.86; H, 9.69.

The infrared spectrum in a Nujol mull indicated a γ-lactone which was identical to the spectrum of the γ-lactone obtained from the electrolyses of I and II.

Isomerization of the *trans*-Lactone of 2-(1-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid (IIIa).—A solution containing 0.500 g. (0.0024 mole) of IIIa and 10 ml. of 0.20 *N* sodium methoxide in 200 ml. of anhydrous methanol was refluxed for 12 hr. according to the general procedure of Asselineau, Bory and Lederer.[20] The solution was neutralized with acetic acid, the methanol distilled, and the remainder of the reaction mixture was submitted to steam distillation. Ether extraction of the distillate gave 0.319 g. (64%) of liquid. The infrared spectrum in carbon disulfide indicated it to be a mixture consisting of 9% of the *trans*- and 91% of the *cis*-lactones of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid.

Preparation of the Lactone of 2-(1-Hydroxycyclohexyl)-1,-4-cyclohexadiene-1-carboxylic Acid (VI).—A solution of 15 g. (0.082 mole) of the methyl ester of β-(1-hydroxycyclohexyl)-propiolic acid[21] and 70 ml. of freshly distilled butadiene in 150 ml. of benzene was heated for 15 hr. at 190–200° in a glass lined bomb according to the general procedure of Joshel and Butz.[22] The benzene was then removed by distillation under reduced pressure to give 46 g. of gummy residue. This material was leached with hot methanol to give 15.47 g. of an oily solid. Recrystallization from petroleum ether (b.p. 30–60°) gave 11.41 g. (68%) of product, m.p. 90–95°. An analytical sample obtained by further recrystallization melted at 96–97°; $\lambda_{\max}^{\text{MeOH}}$ 230 mμ, $\epsilon_{\max}$ 3,800, ϵ 210 mμ 6,900.[23]

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.45; H, 7.80.

The infrared spectrum in Nujol mull indicated an unsaturated γ-lactone.[24]

Preparation of the Lactone of 2-(1-Hydroxycyclohexyl)-1-cyclohexene-1-carboxylic Acid (IXa).—Using 0.50 g. of Adams catalyst, 0.300 g. (0.00147 mole) of VI in 100 ml. of ethanol was reduced at 25° in a Parr reduction apparatus at 3 atmospheres, overnight. The partially reduced material was isolated to give 0.268 g. (89%), m.p. 70–73°. An analytical sample obtained by recrystallization from petroleum ether (b.p. 30–60°) melted at 79–80°, $\lambda_{\max}^{\text{MeOH}}$ 220 mμ, $\epsilon_{\max}$ 11,200.[25]

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.53; H, 8.58.

The infrared spectrum in Nujol mull indicated an unsaturated γ-lactone.[24]

Preparation of the *cis*-Lactone of 2-(1-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid (IIIb).—A solution of 10.74 g. (0.053 mole) of IXa in 500 ml. of ethanol was reduced at 150° under 100 atmospheres of hydrogen using 10 g. of Raney nickel catalyst. The totally reduced material was recovered to give 9.0 g. (82%) of oil which crystallized on standing, m.p. 50–52°. An analytical sample prepared by recrystallizing from petroleum ether (b.p. 30–60°) melted at 55–56°. This compound showed no appreciable ultraviolet absorption between 400 and 215 mμ.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.75; H, 9.70.

The infrared spectrum in Nujol mull indicated a γ-lactone. The spectrum was distinctly different from the spectrum of the *trans* isomer IIIa.

Preparation of the *cis*- *and trans*-Lactone of 2-(1-Hydroxycyclohexyl)-1-hydroxycyclohexanecarboxylic Acid (VIIIa, VIIIb). Using Colonge's β-Ketol.—To a solution of 50 g. (0.252 mole) of 2-(1-hydroxycyclohexyl)-cyclohexanone[7] and 100 g. of potassium cyanide in 500 ml. of ethanol, 100 ml. of glacial acetic acid was added cautiously in a hood according to the general procedure of Boekelheide and Schilling.[26] The mixture was refluxed overnight, the ethanol removed by atmospheric distillation and the remainder of the reaction mixture poured into water. The infrared spectrum of the water-insolubles indicated an imidic acid ester[27] (VII). The aqueous suspension was digested for 3 hr. on a steam-bath and ether extraction of the cooled mixture gave 50 g. (89%) of product. On standing for a week in a refrigerator, 10 g. of a solid, fraction A, m.p. 150–155°, crystallized out. For convenience, the residual liquid will be called fraction B. Fraction A VIIIa was the *trans* isomer; an analytical sample obtained by several recrystallizations from ethyl ether melted at 159–161°. The infrared spectrum in Nujol mull indicated a hydroxyl group as well as a γ-lactone.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.86; H, 8.99.

Fraction B (VIIIb) was the *cis* isomer; this liquid could not be induced to crystallize. The infrared spectrum of a film indicated a hydroxyl group as well as a γ-lactone.

Using Stanek's β-Ketol.—The above procedure was repeated using 50 g. (0.252 mole) of Stanek's β-ketol,[8] m.p. 166.5–167°, which had given an incorrect analysis (*Anal.* Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 75.65, 75.75; H, 9.76, 9.82), to give 51 g. (89%), m.p. 173–175°. An analytical sample obtained by several recrystallizations from benzene melted at 183–184.5°, but again gave an incorrect analysis. The structure of this compound was not

---

[18] E. L. Foreman and S. M. McElvain, THIS JOURNAL, **62**, 1438 (1940).

[19] R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 728 (1951).

[20] C. Asselineau, S. Bory and E. Lederer, *Bull. soc. chim. France*, 1524 (1955).

[21] E. R. Jones and M. C. Whiting, *J. Chem. Soc.*, 1423 (1949).

[22] L. M. Joshel and L. W. Butz, THIS JOURNAL, **63**, 3350 (1941).

[23] S. L. Emerman and J. Meinwald, *J. Org. Chem.*, **21**, 375 (1956). The isolated double bond in 1,4-cyclohexadienyl methyl ketone and 1,4-cyclohexadiene-1-carboxylic acid have been reported to bring about a shift in both wave length and intensity of maximal absorption; 1,4-cyclohexadienyl methyl ketone exhibits a $\lambda_{\max}^{\text{EtOH}}$ at 245 mμ, $\epsilon_{\max}$ 4000, while 1-cyclohexenyl methyl ketone has a $\lambda_{\max}^{\text{EtOH}}$ at 232 mμ, $\epsilon_{\max}$ 12,500. Similarly, 1,4-cyclohexadiene-1-carboxylic acid exhibits a $\lambda_{\max}^{\text{EtOH}}$ at 235 mμ, $\epsilon_{\max}$ 2500, while 1-cyclohexene-1-carboxylic acid has a $\lambda_{\max}^{\text{EtOH}}$ at 212 mμ, $\epsilon_{\max}$ 11,000.

[24] J. F. Grove and H. A. Willis, *J. Chem. Soc.*, 877 (1951).

[25] L. J. Haynes and E. R. H. Jones, *ibid.*, 954 (1946), have reported for the lactone of 2-(1-hydroxycyclohexyl)-acrylic acid λ^{EtOH} 214 mμ, ϵ 10,000.

[26] V. Boekelheide and W. M. Schilling, THIS JOURNAL, **72**, 712 (1950).

[27] The five-membered cyclic imidic acid ester absorption at 5.9 μ disappeared on hydrolysis.

determined, but it was obvious that the desired lactone was not obtained.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 71.99, 72.16; H, 9.07, 9.16.

The infrared spectrum of a Nujol mull indicated a hydroxyl group as well as a γ-lactone.

Preparation of the Lactone of 2-(1-Hydroxycyclohexyl)-6-cyclohexene-1-carboxylic Acid (IXb) from the Dehydration of the *cis*-Lactone of 2-(1-Hydroxycyclohexyl)-1-hydroxycyclohexanecarboxylic Acid (VIIIb).—To a solution of 50 g. (0.223 mole) of VIIIb in 150 ml. of dry pyridine was added, cautiously, 50 ml. of thionyl chloride according to the general procedure of Boekelheide and Schilling.[26] The mixture was heated overnight on a steam-bath, cooled and poured into ice-water. Ether extraction gave 33 g. (72%) of product, m.p. 67–69°. An analytical sample obtained by several recrystallizations from petroleum ether (b.p. 30–60°) melted at 71–72°, $\lambda_{\max}^{\text{MeOH}}$ 220 mμ, $\epsilon_{\max}$ 11,100. The melting point was depressed, m.p. 63–64°, on admixture with IXa. The infrared spectrum in Nujol mull indicated an unsaturated γ-lactone. The spectrum was distinctly different from IXa.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.90; H, 8.54.

Preparation of the Lactone of 2-(1-Hydroxycyclohexyl)-1-cyclohexene-1-carboxylic Acid (IXa) from the Dehydration of the *trans*-Lactone of 2-(1-Hydroxycyclohexyl)-1-hydroxycyclohexanecarboxylic Acid (VIIIA).—To a solution of 2.0 g. (0.0089 mole) of VIIIa in 10 ml. of dry pyridine was added 4 ml. of thionyl chloride. The reaction was carried out as described above to give 1.65 g. (90%) of product, m.p. 68–75°. An analytical sample obtained by several recrystallizations from petroleum ether (b.p. 30–60°) melted at 79–80°. It was found to be identical (mixed melting point 79–80°, ultraviolet and infrared spectra) with IXa obtained from the reduction of the lactone of 2-(1-hydroxycyclohexyl)-1,4-cyclohexadiene-1-carboxylic acid (VI).

Preparation of the *cis*-Lactone of 2-(1-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid (IIIb) from the Reduction of the Lactone of 2-(1-Hydroxycyclohexyl)-6-cyclohexene-1-carboxylic Acid (IXB).—A solution of 33 g. (0.160 mole) of IXb in 500 ml. of ethanol was reduced, using 10 g. of Raney nickel catalyst at 150° and 100 atmospheres of hydrogen. The totally reduced material was recovered to give 25 g. (75%) of an oil which solidified on standing, m.p. 50–52°. An analytical sample obtained by several recrystallizations from petroleum ether (b.p. 30–60°) melted at 55–56° with no appreciable ultraviolet absorption between 400 and 215 mμ. It was found to be identical (mixed melting point, 55–56° and infrared spectra) with IIIb obtained from the reduction of IXa.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68; mol. wt., 208. Found: C, 74.76; H, 9.52; mol. wt., 213 (cryoscopic).

Preparation of *cis*-2-(1-Hydroxycyclohexyl)-cyclohexanemethanol (Vb).—A solution of 1.00 g. (0.0048 mole) of IIIb was reduced with lithium aluminum hydride as described above to give 1.00 g. (98%) of glycol. Recrystallization from hexane gave a solid, m.p. 117–118°.

Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.42; H, 11.12.

The infrared spectrum in a Nujol mull indicated a hydroxyl group and was distinctly different from the spectrum of the *trans* isomer Va.

Isomerization of the *cis*-Lactone of 2-(1-Hydroxycyclohexyl)-cyclohexanecarboxylic Acid (IIIb).—A solution containing 0.104 g. (0.0005 mole) of the *cis*-lactone of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid was isomerized as described for the *trans* isomer to give 0.047 g. (45%) of liquid. The infrared spectrum in carbon disulfide indicated it to be a mixture consisting of 10% of the *trans*- and 90% of the *cis*-lactones of 2-(1-hydroxycyclohexyl)-cyclohexanecarboxylic acid, identical to that obtained from the isomerization of the *trans*-lactone IIIa.

BROOKLYN 1, NEW YORK

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Antispasmodics. IX. 1-Azaspiro[4.5]decane and Derivatives[1]

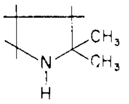
BY ROBERT BRUCE MOFFETT

RECEIVED FEBRUARY 13, 1957

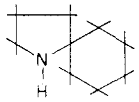
Previous studies in these laboratories have demonstrated that certain compounds containing 2,2-dimethylpyrrolidine (I) are particularly potent anticholinergics. The structurally similar compound, 1-azaspiro[4.5]decane (II), has now been prepared, in which the two methyl groups are joined in a ring. This was incorporated into a variety of compounds of types known to be in general powerful anticholinergics (VIII, IX and XII); however, they had surprisingly little of this type of activity.

A considerable number of compounds containing the pyrrolidine group have been studied in these laboratories.[2] Of these the 2,2-dimethylpyrrolidine group (I) has been found to be particularly potent when combined, for example, in esters of the type generally used in antispasmodics.[2c]

In extending this work we have investigated the effect of joining the two methyl groups in a ring thus creating the spiro structure, 1-azaspiro[4.5]-decane (II).

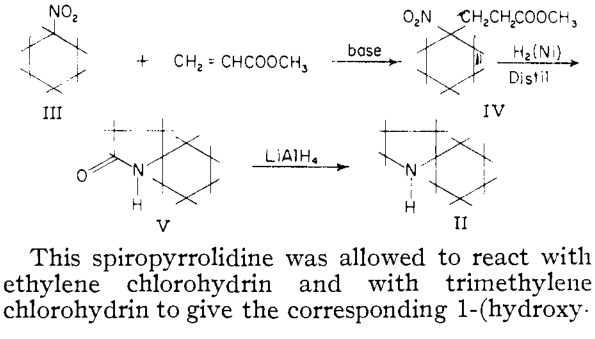


I

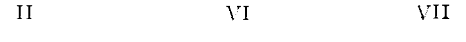


II

This was accomplished by a modification of the synthesis used for 2,2-dimethylpyrrolidine.[2b]



This spiropyrrolidine was allowed to react with ethylene chlorohydrin and with trimethylene chlorohydrin to give the corresponding 1-(hydroxy-



---

(1) Presented before the Division of Medicinal Chemistry, A.C.S., at Atlantic City, New Jersey, September, 1956, Abstracts, page 4-N.

(2) (a) R. B. Moffett, *et al.*, *J. Org. Chem.*, **14**, 862 (1949); (b) **17**, 407 (1952); (c) THIS JOURNAL, **77**, 1565 (1955), and preceding papers in this series.