459. *Unsaturated Lactones and Related Substances. Part II. The Synthesis of Aldehydo-acids by the Rosenmund Reaction.*

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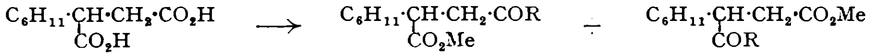
The Rosenmund method for the preparation of aldehydes can be applied to the synthesis of the half-aldehydes of succinic acids. *cyclo*Hexylsuccinic acid gives an inseparable mixture of the two isomeric half-esters which, through the acid chlorides, yields a mixture of the two corresponding aldehydo-esters (α- and β-*cyclo*hexyl-β-formylpropionic ester) which are easily separated through the semicarbazones. The α-*cyclo*hexyl derivative has been independently synthesised from the product of the formylation of *cyclo*hexylsuccinic ester. The β-*cyclo*hexyl derivative is identical with that made by Elderfield and his co-workers by another method. The formylation of an α-substituted succinic ester thus occurs on the unsubstituted carbon atom, contrary to Ranganathan and in agreement with Carrière.

The most important cardiac glycosides, such as those of *digitalis*, contain a characteristic unsaturated γ-lactone group substituted by a steroid residue on the β-carbon but with no γ-substituent. This lactone is formally derived by loss of water from the enolic form of a β-aldehydo-acid. With the object of extending our knowledge of these comparatively inaccessible compounds, we have investigated the partial reduction of succinic acids.

It has been shown (Rosenmund, *Ber.*, 1918, **51**, 585; Rosenmund and Zetzsche, *ibid.*, p. 594; Rosenmund and Zetsche, *ibid.*, 1921, **54**, 425; Zetzsche and Flütsch, *ibid.*, p. 2888; Zetzsche and Enderlin, *ibid.*, 1922, **55**, 609) that acid chlorides can be hydrogenated to aldehydes in the presence of a poisoned palladium catalyst, and that the reaction can be used for the preparation of the dialdehydes of dibasic acids (Zetzsche and Flütsch, *loc. cit.*; Zetsche and Enderlin, *loc. cit.*). We now find that it can be successfully used for the preparation of the corresponding half-aldehydes.

The half-methyl ester, half-chloride of succinic acid yielded succinaldehydic ester in 60% yield.* The product was characterised as the semicarbazone, which was hydrolysed to the known semicarbazone of succinaldehydic acid.

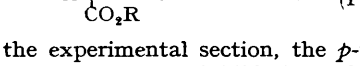
Attention was next turned to the *cyclo*hexylsuccinic acid series in which the alicyclic ring parallels ring D of the steroid skeleton. The parent acid (I) was readily prepared by the interaction of *cyclo*hexyl bromide with the sodium derivative of carbethoxysuccinic ester, followed by hydrolysis. It was hoped that the large unsymmetrical substituent would bring about some distinction between the two carboxyl groups in their ease of esterification (compare Bone, Sudborough, and Sprankling, *J.*, 1904, **85**, 534). The addition of sodium methoxide to the anhydride of (I), however, gave a liquid mixture of the half-esters (II; R = H) and (III; R = H) which could not be separated.



$$\mathrm{C_6H_{11}\cdot\underset{CO_2H}{CH}\cdot CH_2\cdot CO_2H} \longrightarrow \mathrm{C_6H_{11}\cdot\underset{CO_2Me}{CH}\cdot CH_2\cdot COR} + \mathrm{C_6H_{11}\cdot\underset{COR}{CH}\cdot CH_2\cdot CO_2Me}$$

(I.) (II.) (III.)

By the addition of sodium benzyloxide to the anhydride of (I), it was found possible to isolate one of the half benzyl esters as a homogeneous crystalline solid, but in too poor yield for practical purposes. At the time that this work was done (1941), it was not known that the half-esters half-chlorides of unsymmetrically substituted succinic acids could rearrange in the manner which has since been demonstrated by Cason (*J. Amer. Chem. Soc.*, 1947, **69**, 1548) and Ställberg-Stenhagen (*ibid.*, p. 2568). The half methyl esters were accordingly converted into the mixture of half-ester half-chlorides (II and III; R = Cl). This again resisted all attempts at separation of the isomerides. There was no selective decomposition of the two acid chloride groups with either alkalis or *p*-toluidine. In the course of this phase of the work,



$$\mathrm{C_6H_{11}\cdot\underset{CO_2R}{CH}\cdot CH_2\cdot CO\cdot NH\cdot C_7H_7}$$

(IV.)

which is described in detail in the experimental section, the *p*-tolylimide and di-*p*-toluidide of (I) were prepared, and a homogeneous mono-*p*-toluidide (probably IV; R = H) was obtained by the action of *p*-toluidine on the anhydride: it yielded a homogeneous methyl ester.

In view of these difficulties we examined the Rosenmund reduction of the mixed half-ester half-chloride (II and III; R = Cl), in the hope that the separation of the two aldehydo-esters would be simpler. These expectations were realised.

The hydrogenation required a catalyst containing only a trace of the usual sulphur–

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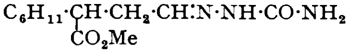
* We are indebted to Dr. James Cason for this experiment.

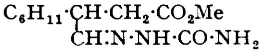
quinoline poison; if the customary amount of poison was added, absolutely no reduction occurred. About half the theoretical amount of hydrogen chloride was liberated rapidly, and a further 20—30% quite slowly. This suggested a possible selective reduction of the two chlorides but attempts to stop the reaction at the half-way stage and separate the aldehyde and unreacted chloride failed, owing to the polymerisation of the former during fractional distillation. For the same reason it was found desirable to carry the reaction to completion, distil the aldehyde rapidly under reduced pressure and convert it at once into semicarbazone. The yield of semicarbazone (V and VI) is 90% and the overall yield in the 6-stage synthesis from *cyclo*hexylcarbethoxysuccinic ester is over 50%.

The semicarbazone had an indefinite melting point but was easily separated into two isomeric components, melting at 151° and 118—119°. These substances undoubtedly have the structures (V) and (VI), respectively.



$C_6H_{11}\cdot\underset{CO_2Me}{CH}\cdot CH_2\cdot CH{:}N\cdot NH\cdot CO\cdot NH_2$

(V.), m. p. 151°

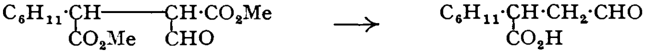


$C_6H_{11}\cdot\underset{CH{:}N\cdot NH\cdot CO\cdot NH_2}{CH}\cdot CH_2\cdot CO_2Me$

(VI.), m. p. 118—119°

While this work was in progress Elderfield and his co-workers described some related syntheses (Fried, Rubin, Paist, and Elderfield, *Science*, 1940, **91**, 435; Rubin, Paist, and Elderfield, *J. Org. Chem.*, 1941, **6**, 260; Paist, Blout, Uhle, and Elderfield, *ibid.*, p. 273). In the course of this they prepared the ester-semicarbazone (VI) by a method which left little doubt as to the structure. Through the kindness of Professor R. C. Elderfield we have compared the derivatives formed by the two methods. Elderfield's compound melted at 119—119·5° and a direct comparison proved its identity with ours.

The structure of the second isomeride was proved as follows: the dimethyl ester of *cyclo*hexylsuccinic acid was formylated by means of ethyl formate and sodium ethoxide, following the general method of Wislicenus, Böklen, and Reuthe (*Annalen*, 1908, **363**, 340). The product gave every indication of being a mixture of the true formyl ester (VII) and its enolic isomeride. Hydrolysis and decarboxylation of (VII) to the desired aldehydo-acid proved difficult, as is generally true for substances of this class (Carrière, *Ann. Chim.*, 1922, **17**, 38; Ranganathan, *J. Indian Chem. Soc.*, 1939, **16**, 107). The best results were obtained by using aqueous oxalic acid at 100°. The aldehydo-acid (VIII) [which may exist wholly or partly in the lactol form (Carriere, *loc. cit.*; Blaise and Courtot, *Bull. Soc. chim.*, 1906, **35**, 989)] yielded a semicarbazone of m. p. 175°. This on treatment with diazomethane gave the semicarbazone of the corresponding methyl ester (V), m. p. 150°. This was identical with the high-melting isomeride from the Rosenmund reaction. The identity was confirmed by the preparation from both samples of the semicarbazone of the same 2 : 4-dinitrophenylhydrazone.



$C_6H_{11}\cdot\underset{CO_2Me}{CH}\text{———}\underset{CHO}{CH}\cdot CO_2Me \longrightarrow C_6H_{11}\cdot\underset{CO_2H}{CH}\cdot CH_2\cdot CHO$

(VII.) (VIII.)

This work proves that the formylation of the ester of a monosubstituted succinic acid (such as I) occurs on the methylene group. This was assumed by Carrière (*loc. cit.*) in his investigation of the corresponding derivatives of ethylsuccinic acid and is clearly to be expected on general grounds. Ranganathan (*loc. cit.*) has, however, taken the opposite view. He investigated the formylation of *cyclo*pentylsuccinic ester and interpreted the reaction as proceeding on the substituted carbon atom, so that the final product would be β-formyl-β-*cyclo*pentylpropionic acid (type VI and not type V). The present work shows this view to be mistaken, and the structural formulæ proposed by Ranganathan require correction in this respect. Ranganathan also carried out some preliminary experiments in the *cyclo*hexane series but does not appear to have proceeded beyond the anhydride of the parent acid (I). Since this work was completed Swain, Todd, and Waring (*J.*, 1944, 548) have described the formylation of *cyclo*hexylsuccinic ester and have given the products the structures (VII) and (VIII) by analogy with the formylation of phenylsuccinic ester. These structures are now proved.

Only preliminary work was possible on the lactonisation of the aldehydo-acids described in this paper, but similar studies have been described by Elderfield, Todd, and their collaborators (*locc. cit.*).

EXPERIMENTAL.

(All m. p.s are corrected.)

Methyl β-Formylpropionate.—Succinic half methyl ester acid chloride was prepared by the action of phosphorus oxychloride on the sodium salt (Michaelis and Hermens, *Ber.*, 1892, **25**, 2747). The latter compound was prepared by the action of sodium methoxide on succinic anhydride as in the case of the *cyclo*hexyl analogue described below. The acid chloride (12·7 g.), b. p. 84—85°/14—15 mm., in 50 c.c. of xylene was reduced in the presence of 2 g. of palladium–barium sulphate catalyst and 40 mg. of sulphur–quinoline poison. The reaction was conducted at 110° (bath temp.) with vigorous agitation (Hershberg stirrer) according to Cason and Hershberg (*Org. Synth.*, **21**, 87). After 90% of the hydrogen chloride had been liberated (2½ hours) the mixture was cooled, treated with charcoal, filtered, and distilled. The aldehyde (5·9 g.) boiled at 69—70°/14 mm. It reduced Tollens's reagent and Fehling's solution, formed a bisulphite addition compound, and yielded the *semicarbazone* of methyl β-formylpropionate, which formed large colourless prisms, m. p. 130—131°, from methanol (Found: C, 41·3; H, 6·2. $C_8H_{11}O_3N_3$ requires C, 41·6; H, 6·4%).

When the semicarbazone was suspended in N-sodium hydroxide solution it gradually went into solution and the semicarbazone of the corresponding acid was precipitated on the addition of mineral acid. This compound crystallized in small, well defined, colourless prisms, m. p. 190—191° (decomp.) (Carrière, *loc. cit.*, gives m. p. 194—195°).

1 : 1 : 2-*Tricarbethoxy*-1-cyclo*hexylethane*.—The sodium salt of carbethoxysuccinic ester was prepared by adding 147·0 g. of the ester (Bischoff, *Annalen*, 1882, **214**, 38) to a cooled solution of 13·7 g. of sodium in excess of absolute alcohol. After the alcohol had been removed at the water-pump, the residue was dried at 100°/2 mm. for two days. The powdered sodium derivative (154 g.) was boiled under reflux with 182 g. of *cyclo*hexyl bromide in 230 c.c. of dry xylene for 19 hours. The solution was cooled, washed well with water, and dried (Na_2SO_4), and the xylene and excess of *cyclo*hexyl bromide were removed at the water-pump. Fractionation of the residue yielded 112 g. of material, b. p. 143—158°/1—2 mm., and after redistillation, 91 g. of b. p. 195—198°/13—14 mm. (50%).

cyclo*Hexylsuccinic Acid* (I).—This acid was prepared by refluxing a mixture of 31·7 g. of the above ester, 300 c.c. of concentrated hydrochloric acid, and 10 c.c. of alcohol for 48 hours. The acid crystallised directly from the cold solution; yield 19·1 g. (99%), m. p. 144—146°. It crystallised from ether–light petroleum in small colourless prisms, m. p. 144—145° (Swain, Todd, and Waring, *loc. cit.*, give m. p. 146—147° for acid made by a different method). The preliminary condensation is much more efficient when carried out in this way than in boiling alcohol, for which Ranganathan (*loc. cit.*) quotes a yield of 25% of an ester, giving a 67% yield of the acid (I).

The anhydride was distilled from a mixture of 10·0 g. of the acid and 25 c.c. of acetic anhydride which had been heated for two hours on the steam-bath. It boiled at 164—165°/8 mm. and solidified to a white crystalline solid, m. p. 34·5—35·5°; yield, 8·9 g. (97%). From ether–light petroleum it formed large colourless tablets, m. p. 35—36° (Ranganathan gives m. p. 42°). The *acid*-p-*toluidide* (probably IV; R = H), formed by addition of an equivalent quantity of *p*-toluidine to the anhydride in benzene, was purified by solution in aqueous sodium hydrogen carbonate, precipitation with acid, and crystallisation from dilute alcohol. It formed colourless needles melting with decomposition at 187—188°, when the capillary was heated very slowly (Ranganathan, m. p. 187°). By treatment of the acid-*p*-toluidide with diazomethane in ether the *methyl ester* p-*toluidide* (probably IV; $R = CH_3$) was formed quantitatively. From dilute alcohol it yielded colourless needles, m. p. 120—121° (Found: C, 71·4; H, 8·1. $C_{18}H_{25}O_3N$ requires C, 71·25; H, 8·3%).

cyclo*Hexylsuccinic Half Methyl Ester* (II and III; R = OH).—A standard solution of sodium methoxide in methanol (0·816N.; standardised against potassium acid phthalate) (135 c.c.) was added to a chilled suspension of *cyclo*hexylsuccinic anhydride (19·95 g.) in methanol. The alcohol was then removed at 40° (water-pump), and the crystalline residue of sodium salt was dissolved in water, and the solution filtered, washed once with ether, and treated with a slight excess of hydrochloric acid. The precipitated oily half-ester was taken up in ether, washed with water, and dried first over sodium sulphate and finally, after removal of the solvent, in a vacuum desiccator (Found: on two different samples, equiv., 219, 212·2. Calc.: 214·2).

When submitted to vacuum distillation the half-ester partially decomposed into methanol and the anhydride, indicated by a depression of the equivalent. Also, when distilled material was converted into the acid chloride, some dichloride, evidently arising from anhydride, appeared to be present, since a *di*-p-*toluidide* was isolated on treatment with *p*-toluidine. From methanol it formed long felted needles, m. p. 250—250·5° (without decomp.) (Found: N, 7·7. $C_{24}H_{30}O_2N_2$ requires N, 7·4%).

The half benzyl ester was prepared by treating the anhydride with sodium benzyloxide prepared according to Bischoff (*Ber.*, 1903, **36**, 159) by heating equivalent quantities of sodium and benzyl alcohol in benzene. The formation of sodium benzyloxide was incomplete and consequently the yield of half-ester was diminished. On long storage the oily ester deposited some crystals which were triturated with light petroleum and recrystallised from ether–light petroleum; bold colourless prisms, m. p. 60—61°.

cyclo*Hexylsuccinic half methyl ester acid chloride* (II and III; R = Cl) was prepared by treating the above half methyl ester with an excess of thionyl chloride, purified according to Fieser (" Experiments in Organic Chemistry," D. C. Heath and Co., 1935). Next morning the mixture was warmed to 40—50° for one hour and fractionated. The acid chloride distilled at 117—118°/2—3 mm. as a colourless liquid; yield, 23·4 g. (91·5% from anhydride) (Found: Cl, 15·3. $C_{11}H_{17}O_3Cl$ requires Cl, 15·2%).

A mixture of ester *p*-toluidides was formed by treatment of the acid chloride in acetone with an excess of *p*-toluidine. On addition of dilute hydrochloric acid the crude *p*-toluidides separated as an oil and solidified when scratched. After crystallisation the material formed colourless felted needles from dilute alcohol, melting indefinitely between 130° and 140°. A sample was treated with alcoholic aqueous alkali for two hours at room temperature. After dilution with water a solid residue was filtered off. It crystallised from dilute alcohol in glistening colourless needles. This material, m. p. 164·5—165°, was identical with a sample of the *p*-tolylimide prepared by vacuum distillation of the acid *p*-toluidide obtained by addition of *p*-toluidine to the anhydride as described above.

The crude mixture of acid *p*-toluidides was precipitated from the aqueous solution (after the removal of the tolylimide) by the addition of mineral acid. After dissolution in and reprecipitation from bicarbonate solution, the recrystallised material formed colourless needles from dilute alcohol, and had m. p. 187—188° (decomp.) when heated very slowly. No depression was observed on mixing with a sample of the homogeneous acid *p*-toluidide (VII; R = H) obtained above. However, the new material cannot be homogeneous because methylation with diazomethane regenerated a mixture of ester *p*-toluidides, m. p. *ca.* 125—140°, similar to that described above.

*Methyl β-Formyl-α-*cyclo*hexylpropionate.*—The mixture of acid chlorides (II and III; R = Cl) (8·7 g.) in 40 c.c. of dry xylene was reduced according to the same procedure as used for the succinic acid derivative in the presence of 1 g. of catalyst and 3 mg. of poison.* The bath-temperature did not exceed 114°. In 1½ hours 50% of the hydrogen chloride was liberated, and in the next 1½ hours a further 27%. The reaction had then almost ceased. The mixture was cooled, treated with Norite, filtered, and fractionated. The aldehyde distilled at 124—130°/4—5 mm. as a colourless liquid; yield 5·4 g. (73%). This was immediately added to a methanol solution of semicarbazide, prepared by warming a suspension of equal weights of semicarbazide hydrochloride and sodium hydrogen carbonate in methanol at 40° until all the carbon dioxide was evolved, and filtering off the sodium chloride. On the addition of water the mixture of semicarbazones crystallised; yield, 6·1 g. (88·5%), m. p. *ca.* 104—128°. When the mixture was crystallised slowly from dilute methanol the less soluble isomeride separated in colourless microscopic rods, m. p. 150—151°; yield, 2·8 g. After one recrystallisation the *semicarbazone* of *methyl β-formyl-α-*cyclo*hexylpropionate* (V) melted constantly at 150·5—151° (Found: C, 56·6; H, 8·1. $C_{12}H_{21}O_3N_3$ requires C, 56·45; H, 8·3%).

The concentrated mother-liquor yielded on standing overnight the isomeric semicarbazone, 2·5 g., m. p. 110—115°. One recrystallisation from dilute alcohol gave 1·9 g. of needles, m. p. 114—117°. A sample recrystallised several times yielded the pure semicarbazone of methyl β-formyl-β-*cyclo*hexylpropionate (VI), m. p. 118—119°. A mixed melting point with a sample of Elderfield's semicarbazone (m. p. 118—119°) showed no depression.

Formylation of cyclo*Hexylsuccinic Ester.*—Dimethyl *cyclo*hexylsuccinate was prepared by refluxing 39 g. of the acid (I) with 150 c.c. of methanol and 6 c.c. of sulphuric acid for 6 hours. Isolated as usual, the ester boiled at 122—125°/2 mm.; yield, 40 g., 89%.

Anhydrous alcohol (13 c.c.) was added to 200 c.c. of dry ether containing 5 g. of sodium wire. At the end of the reaction (overnight) a mixture of 40 g. of the above ester and 17 g. of freshly distilled ethyl formate was added. After 2 days at room temperature, the product was decomposed with 50 g. of ice and 60 c.c. of 20% sulphuric acid. The aqueous layer was removed and extracted with ether. The united ethereal solution was then extracted with three successive portions of 50 c.c. of cold saturated aqueous potassium carbonate. The aldehydic ester was recovered from the alkaline extract by acidification, ether extraction, and distillation. The product (VII) was a viscous oil boiling over a considerable range (compare Carrière, *loc. cit.*) but mainly in the range 145—155°/2—3 mm. All fractions gave a red colour with alcoholic ferric chloride. This was most intense with the lower-boiling fractions, which presumably contained most of the enol. When the ethereal layer which had been extracted with carbonate was allowed to stand for two days and was again extracted with potassium carbonate, a further quantity of the formyl ester was recovered, indicating the formation of more enolic material on standing. Total yield: 14·4 g. (32%).

*β-Formyl-α-*cyclo*hexylpropionic Acid* (VIII).—The formyl ester (VII) (2 g.) was heated with 1·5 g. of oxalic acid and 5 c.c. of water for 5 hours in a slow current of steam, by which time the evolution of carbon dioxide had ceased. The residue was extracted with ether, and the extract washed with calcium acetate solution and water, and dried (Na_2SO_4). The residue from the ether distilled between 130° and 155°/2—3 mm. as a viscous oil which was converted into a *semicarbazone* in the usual way. This separated at 0° as a flocculent precipitate which after crystallisation from dilute alcohol had m. p. 175—175·4°; yield 0·3 g. (16%). It was soluble in aqueous sodium carbonate but insoluble in water (Found: C, 55·3; H, 7·9. $C_{11}H_{19}O_3N_3$ requires C, 54·8; H, 7·9%).

The semicarbazone was esterified with diazomethane in methanol. It yielded the methyl ester semicarbazone (V) which melted at 149—150° alone or mixed with the corresponding substance prepared through the Rosenmund method.

Samples of the ester-semicarbazone prepared by both procedures were warmed with an alcoholic solution of 2:4-dinitrophenylhydrazine. The yellow crystals so formed were then recrystallised from alcohol. Both products melted at 132—133° after a partial melting at 111—112°. After a further crystallisation from acetic acid the pure 2:4-*dinitrophenylhydrazone* of *methyl β-formyl-α-*cyclo*hexylpropionate* was obtained from both samples, melting sharply at 132·5—133° (Found: C, 54·2; H, 5·8. $C_{17}H_{22}O_6N_4$ requires C, 54·0; H, 5·9%).

Hydrolysis of the formyl ester (VII) with hydrogen bromide in acetic acid yielded *cyclo*hexylsuccinic acid (m. p. 143—144°) and an unsaturated lactone not yet fully investigated. This lactonisation has since been studied by Swain, Todd, and Waring (*loc. cit.*).

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* It seems necessary to determine the optimum amounts of catalyst and poison before the reduction is started. The introduction of additional catalyst after the reaction is in progress has no apparent effect on the rate of reduction. Thus, when the components were mixed with too much poison to permit any reduction to begin, additional catalyst did not serve to initiate the reaction.