[CONTRIBUTION NO. 285 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY AND ENZYMOLOGY, FORDHAM UNIVERSITY]

Studies on the Chemistry of Heterocyclics. XXVI. Investigations on the Prototropic Rearrangement of γ-Hydroxyacetylenic Esters and Acids in the Thiophene Series

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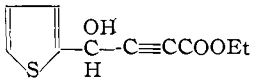
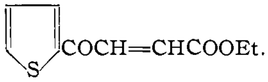
RECEIVED OCTOBER 19, 1953

The preparation of γ-hydroxyacetylenic esters and acids is described. The properties of some of the intermediates have been studied. It has been found that under certain conditions the acetylenic ester  undergoes a novel prototropic rearrangement to give the compound .

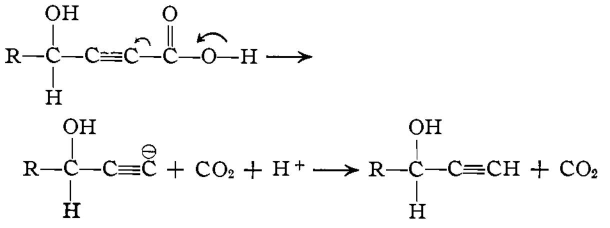
Due to their importance for the elucidation of the structure and synthesis of natural products, acetylenic acids have been thoroughly investigated during recent years.[1] However, the corresponding acids in the heterocyclic series have received only passing mention.[1]

The now readily available ethynylcarbinols in the thiophene series[2] allowed us to investigate the preparation and lactonization as well as the prototropic rearrangement of these acids and their respective esters in the thiophene series.

The most convenient method for the preparation of these acids appeared to be the carbonation of the sodium salts of the readily available ethynylcarbinols. Such preparation methods were successfully applied in the aromatic series.[3,4]

Due to the fact that decarboxylation of the acetylenic acids proceeds much more easily than the decarboxylation of the corresponding ethylenic or saturated acids, the direct carbonation of the sodium salts or Grignard complexes is more difficult.

This fact is related to the enhanced acid strength of the acetylenic acids and to the partial *m*-directing influence of the propiolic acid group.[5a,b] To minimize this effect we attempted to carbonate the corresponding sodium salts and Grignard complexes of 2-thienylethynyl- and 3-methyl-2-thienylethynylcarbinols with Dry Ice under pressure. However, none of the desired acids could be obtained. When various solvents such as benzene, toluene or mixtures of benzene and ether were applied,[6] the yields of the corresponding acids in the benzene series could be substantially increased. When applied to the thiophene series these variations did not lead to the desired γ-hydroxyacetylenic acids.



$$R-\underset{H}{\overset{OH}{C}}-C\equiv C-\overset{O}{\overset{\|}{C}}-O-H \longrightarrow$$

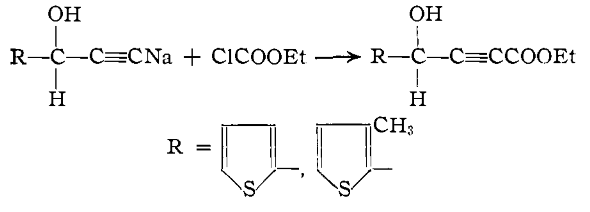
$$R-\underset{H}{\overset{OH}{C}}-C\equiv \overset{\ominus}{C} + CO_2 + H^+ \longrightarrow R-\underset{H}{\overset{OH}{C}}-C\equiv CH + CO_2$$

However, very small yields of thiophene-2-carboxylic acid and 2-thienylglyoxalic acid were obtained. It seems that the γ-hydroxyacetylenic acids in the thiophene series are easily hydrated under the conditions of the reaction and the keto acids obtained are easily cleaved, thus furnishing the above mentioned acids. The occurrence of such a cleavage in alkaline medium was observed earlier.[7] The cleavage of the keto acid obtained on hydration of the triple bond takes place as

$$RC\equiv CCOOH \longrightarrow [RCOCH_2COOH] \longrightarrow RCOOH + CH_3COOH$$

It was concluded that the direct carbonation method was not suitable in this series.

Another possibility was to use the sodium salts[8] of the corresponding ethynylcarbinols in the thiophene series and try to combine them with ethyl or methyl chlorocarbonates in non-polar or weakly polar solvents such as ether.[9] The reaction would proceed as



$$R-\underset{H}{\overset{OH}{C}}-C\equiv CNa + ClCOOEt \longrightarrow R-\underset{H}{\overset{OH}{C}}-C\equiv CCOOEt$$

Unfortunately, when the original method was applied in the thiophene series, the sodium salts of the corresponding ethynylcarbinols were obtained in an unreactive form, consequently slowing down the reaction appreciably. However, applying sodium amide in liquid ammonia for the preparation of the sodium salts and replacing the liquid ammonia as rapidly as possible by a non-polar solvent and elevating the temperature, the sodium salts of the ethynylcarbinols were obtained in an active form and furnished the esters of γ-hydroxyacetylenic acids in good yield. It has been shown earlier[10] that analogous acetylenic hydroxyesters react readily with diethylamine to give highly crystalline diethylaminolactones. The corresponding acetylenic

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* Condensed from a portion of the Dissertation of A. V. submitted to the Graduate School of Fordham University in partial fulfillment of the requirements of the Ph.D. degree.

(1) A. W. Johnson, "The Chemistry of the Acetylenic Compounds. Vol. II. The Acetylenic Acids." Longmans, Green and Co., New York, 1950; W. Reppe, *et al.*, *Ann.*, **582**, 1 (1953).

(2) A. Vaitiekunas, R. E. Miller and F. F. Nord, *J. Org. Chem.*, **16**, 1603 (1951).

(3) R. A. Raphael, *J. Chem. Soc.*, 805 (1947).

(4) A. W. Nineham and R. A. Raphael, *ibid.*, 119 (1949).

(5) (a) J. W. Baker, K. E. Cooper and C. K. Ingold, *ibid.*, 426 (1928); (b) K. Koessler and M. T. Hanke, *J. Biol. Chem.*, **50**, 193 (1922).

(6) L. J. Haynes and E. R. H. Jones, *J. Chem. Soc.*, 503, 954 (1946).

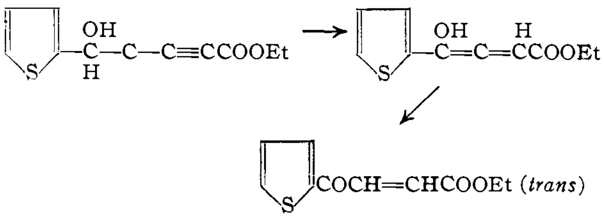
(7) A. Corbellini, F. Capuci and G. Tomassini, *Gazz. chim. ital.*, **69**, 137 (1939), quoted from ref. (1) and *C. A.*, **33**, 7780 (1939).

(8) J. U. Nef, *Ann.*, **308**, 326 (1899).

(9) C. Moureu and R. Delange, *Compt. rend.*, **136**, 552 (1903).

(10) E. R. H. Jones and M. C. Whiting, *J. Chem. Soc.*, 1423 (1949).

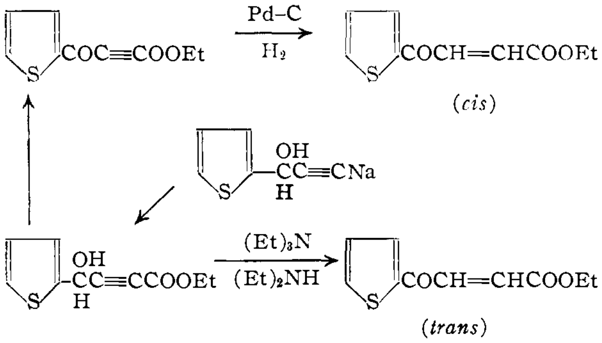
esters in the thiophene series reacted exothermally with an excess of diethylamine, but the reaction product was an oil. Analogous observations were made earlier.[4] On distillation there was obtained a yellowish oil which should be the *trans* form of ethyl β-2-thenoylacrylate according to its ultraviolet absorption spectrum when compared with the corresponding benzene derivative (by analogy). The yield was 24%. The attempted isolation of the corresponding lactone was unsuccessful. As the prototropic rearrangement appeared worthy of study in the thiophene series, and to obviate the complication caused by the addition to the triple bond, the reaction was carried out in the presence of a tertiary amine. This time the yield of the product was 84%. The mechanism of the reaction could be represented by considering that an allene structure functions as an intermediate



To prove that this was really the *trans* form of ethyl thenoylacrylate, the ethyl 4-hydroxy-4-(2-thienyl)-2-butynoate was successfully oxidized to ethyl β-thenoylpropiolate by means of chromic acid (CrO_3) in acetone. The structure of that compound was confirmed by obtaining its 2,4-dinitrophenylhydrazone derivative. Ethyl β-thenoylpropiolate on semi-hydrogenation furnished the *cis*-ethyl β-thenoylacrylate the elemental analysis of which corresponded to that of the *trans* form previously obtained; however, its λ_{max} was shifted appreciably to the visible (λ_{max} 260, ϵ 12,700).

The very similar prototropic rearrangement of α-hydroxyethylenes to saturated ketones is well known.[11-13] These reactions were carried out and are summarized in Chart 1.

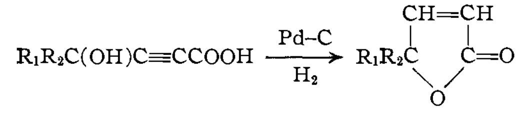
CHART 1



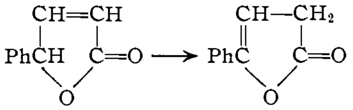
The free 4-hydroxy-4-(2-thienyl)-2-butynoic acid was obtained on saponification with sodium hydroxide in benzene solution. In general, the hydrolysis of the acetylenic esters is effected by the normal method of refluxing with an alcoholic solution of potassium hydroxide. However, the conditions of hydrolysis must not be too vigorous, otherwise cleavage of the molecule occurs.[14]

When the temperature of hydrolysis was increased up to 70° and 5% alcoholic potassium hydroxide was utilized for saponification, most of the acetylenic ester polymerized and no free acetylenic acid could be isolated. However, when the hydrolysis was carried out at room temperature in benzene solution and with aqueous sodium hydroxide, the yields were small and most of the starting material was recovered. But a prolonged treatment under these conditions gave the free γ-hydroxyacetylenic acids in the thiophene series in satisfactory yields.

It was observed earlier[1] that on semi-hydrogenation the γ-hydroxyacetylenic acids cyclize readily to the corresponding lactones



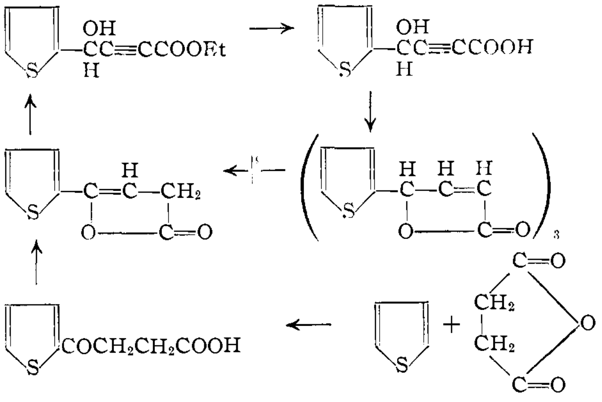
The most interesting case was observed with 3-hydroxy-3-phenyl-1-propyne-1-carboxylic acid,[4] where the lactone formed rearranged as



An analogous reaction could be expected with the corresponding acetylenic acid in the thiophene series.

On catalytic semi-hydrogenation the acid furnished a yellow substance, the elemental analysis of which corresponded to that of the expected lactone. However, when the analogous lactone was synthesized starting from thiophene with succinic anhydride *via* the 2-thenoylpropionic acid by means of acetic anhydride (as shown in Chart 2), it had a lower melting point and its ultraviolet and infrared absorption were not identical with the compound obtained on semi-hydrogenation of the corresponding γ-hydroxyacetylenic acid, as shown in the Experimental part below.

CHART 2



It seems that the lactone does not rearrange but

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(11) R. Rambaud and H. L. Dondon, *Compt. rend.*, **223**, 381 (1946).

(12) M. Tiffeneau, *Bull. soc. chim.*, **1**, 1207 (1907).

(13) M. Hiroshi Nomura, *ibid.*, **37**, 1245 (1925).

(14) C. Moureu and R. Delange, *Compt. rend.*, **132**, 1121 (1901); *Bull. soc. chim.*, **29**, 648, 672, 678 (1903

trimerizes on hydrogenation. The ease of dimerization and trimerization of acetylenic compounds in the thiophene series is very characteristic and was also observed with certain acetylenic alcohols and diacetylenic glycols.[2,15]

The ultraviolet absorption spectra of the compounds studied are summarized in Table I.

TABLE I

ULTRAVIOLET ABSORPTION DATA IN ETHANOL

Compound	$\lambda_{max.}$ mμ	ε
Ethyl 4-hydroxy-4-(2-thienyl)-2-butynoate	233	8,900
Ethyl 4-hydroxy-4-(3-methyl-2-thienyl)-2-butynoate	234	6,700
Ethyl β-2-thenoylpropiolate	230	9,800
Ethyl β-2-thenoylacrylate (*trans*)	235	12,700
Ethyl β-2-thenoylacrylate (*cis*)	260	12,700
4-Hydroxy-4-(2-thienyl)-2-butenoic acid lactone (prepared from 2-thenoylpropionic acid)	282	10,600
4-Hydroxy-4-(2-thienyl)-2-butenoic acid lactone? (obtained on semi-hydrogenation)	262	8,200

The maximum absorptions exhibited by *trans*- and *cis*-ethyl β-2-thenoylacrylate show that these compounds possess the straight chain configuration as designated. As observed earlier, it is analogous with the corresponding benzene derivatives.[4] Lutz and Scott[16] arrived at similar conclusions. In the aliphatic series acetylacrylic esters and acids possess a cyclic structure as indicated by ultraviolet absorption spectra.[17]

Experimental

Materials.—The thiophene used in this work was obtained through the courtesy of the Monsanto Chemical Co., Inc., St. Louis, Mo. The acetylenic carbinols were prepared as earlier described[2] and the ethyl chlorocarbonate was a commercial product.

Ethyl 4-Hydroxy-4-(2-thienyl)-2-butynoate.—To freshly prepared sodium amide (0.055 mole) in 350 ml. of liquid ammonia in a three-neck flask there was added dropwise 0.05 mole of 2-thienylethynylcarbinol dissolved in a threefold volume of absolute ether. After stirring for an additional 15 minutes the liquid ammonia was allowed to evaporate on a steam-bath while replacing it by absolute ether. The reflux of the latter indicated the complete removal of the liquid ammonia. The contents of the flask were cooled to 0–5° and 0.055 mole of ethyl chlorocarbonate dissolved in 35 ml. of absolute ether was added slowly. The reaction mixture turned from red-brown to pale yellow. It was allowed to reach room temperature and was stirred for an additional 2 hours and finally refluxed for one-half hour. The sodium chloride was filtered off, the filtrate washed with 5% sodium bicarbonate solution and finally twice with ice-water and dried over anhydrous sodium sulfate. On fractionation it furnished 7.0 g. (yield 58%) of a slightly yellowish oil, boiling at 154° (22 mm.), $n^{20}{}_{D}$ 1.5130.

Anal. Calcd. for $C_{10}H_{10}O_3S$: C, 57.2; H, 4.8. Found: C, 57.47; H, 4.7.

Ethyl 4-Hydroxy-4-(3-methyl-2-thienyl)-2-butynoate.—The procedure is analogous to that described for ethyl 4-hydroxy-4-(2-thienyl)-2-butynoate. 9.9 g. (0.0065 mole) of 3-methyl-2-thienylethylnylcarbinol furnished 10 g. (yield 65%) of the above ester, b.p. 122° (1 mm.), $n^{20}{}_{D}$ 1.5115.

Anal. Calcd. for $C_{11}H_{12}O_3S$: C, 59.0; H, 5.3. Found: C, 59.2; H, 5.4.

Ethyl β-2-Thenoylpropiolate.—3.3 g. (0.0133 mole) of ethyl 4-hydroxy-4-(2-thienyl)-2-butynoate was dissolved in 50 ml. of acetone and oxidized with chromic acid (CrO_3) in a nitrogen atmosphere while adding a solution of 1.93 g. (0.0052 mole) of chromic acid (CrO_3) dissolved in 1.6 ml. of concd. sulfuric acid and 7 ml. of water. The reaction mixture was kept at 0–5° with continuous stirring for two hours, then diluted with 200 ml. of water and extracted with ether. The ethereal extract was washed with 5% sodium bicarbonate solution and then with ice cold water and dried over anhydrous sodium sulfate. The solvent was then allowed to evaporate. On treatment with 2,4-dinitrophenylhydrazine in the usual manner, the extract furnished the corresponding phenylhydrazone which when recrystallized from dilute acetic acid had a m.p. 171°.

Anal. Calcd. for $C_{16}H_{12}N_4O_6S$: C, 49.5; H, 3.1; N, 14.4. Found: C, 49.5; H, 2.95; N, 14.7.

***cis*-Ethyl β-2-Thenoylacrylate.**—4.7125 g. (0.024 mole) of ethyl β-2-thenoylpropiolate was dissolved in 30 ml. of methanol. Upon addition of 0.4 g. of palladium-on-charcoal (5%) the reaction mixture was shaken until 1 mole of hydrogen had been taken up (555 ml. of H_2 at 22° and 755 mm.). On evaporation of the solvent a yellowish oil was obtained which boiled at 90–93° (3 mm.) on fractionation, λ_{max} 260, ε 12,700.

Anal. Calcd. for $C_{10}H_{10}O_3S$: C, 57.2; H, 4.80; S, 15.3. Found: C, 57.4; H, 4.9; S, 15.2.

***trans*-Ethyl β-2-Thenoylacrylate.**—To a solution of ethyl 4-hydroxy-4-(2-thienyl)-2-butynoate (5 g., 0.042 mole) in 15 ml. of dry ether there was added slowly 15 ml. of triethylamine. After the initial exothermic reaction was over, the mixture was left standing at room temperature overnight. The excess of triethylamine was distilled off and the residual liquid fractionated *in vacuo*. The fraction boiling at 106–108° (3 mm.) analyzed as ethyl β-thenoylacrylate and had the ultraviolet absorption spectrum: λ_{max} 235, ε 12,700; yield 4.2 g. (84%).

Anal. Calcd. for $C_{10}H_{10}O_3S$: C, 57.2; H, 4.80; S, 15.3. Found: C, 57.4; H, 4.69; S, 15.4.

Treatment of ethyl 4-hydroxy-4-(2-thienyl)-2-butynoate with diethylamine gave the same product. However, no corresponding aminolactone could be isolated.

4-Hydroxy-4-(2-thienyl)-2-butynoic Acid.—One gram (0.0047 mole) of ethyl 4-hydroxy-4-(2-thienyl)-2-butynoate was dissolved in 15 ml. of benzene and to this solution 25 ml. of 1.25 *N* sodium hydroxide was added and the reaction mixture shaken at room temperature for 48 hours. Isolation of the acid in the usual manner furnished 0.5 g. of the free acid (yield 57%). When recrystallized from benzene–petroleum ether it melted at 104°.

Anal. Calcd. for $C_8H_6O_3S$: C, 52.8; H, 3.4. Found: C, 53.0; H, 3.6.

S-Benzylthiuronium Salt of 4-Hydroxy-4-(2-thienyl)-2-butynoic Acid.—The salt was prepared in the usual manner. When recrystallized from dilute ethanol it melted at 165°.

Anal. Calcd. for $C_{16}H_{16}O_3N_2S_2$: N, 8.1. Found: N, 8.4.

Semi-hydrogenation of 4-Hydroxy-4-(2-thienyl)-2-butynoic Acid.—0.535 g. (0.00294 mole) of the above acid was dissolved in 30 ml. of methanol. 5% (0.01 g.) of palladium-on-charcoal was added to this solution and the solution shaken in a hydrogenation apparatus until 1 mole of hydrogen was consumed. After filtration and evaporation of the solvent under reduced pressure a yellowish substance resulted which melted at 102° on recrystallization from benzene petroleum ether; λ_{max} 262, ε 8,208; molecular weight, 600 ± 24.

Anal. Calcd. for $C_8H_6O_2S$: C, 57.9; H, 3.6. Found: C, 58.0; H, 3.9.

4-Hydroxy-4-(2-thienyl)-2-butynoic Acid Lactone. (**β,γ-(2-Thienyl)-butenolactone**).—Thenoylpropionic acid[18] (9.3 g., 0.049 mole) was heated with 8 g. (0.075 mole) of acetic anhydride on a steam-bath for 3 hours. The liquid turned red-brown. The excess of acetic anhydride was decomposed with water and on cooling the red oil solidified. It was filtered off. On repeated recrystallization from ethanol yellow brown needles were obtained, m.p. 74–75°; ultraviolet absorption: λ_{max} 282, ε 10,600; infrared absorption: 5.50–5.55 μ.

Anal. Calcd. for $C_8H_6O_2S$: C, 57.9; H, 3.67. Found: C, 57.7; H, 4.0.

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[15] A. Vaitiekunas and F. F. Nord, **THIS JOURNAL**, **76**, 2733 (1954).

[16] R. E. Lutz and G. W. Scott, *J. Org. Chem.*, **13**, 285 (1948).

[17] E. Shaw, THIS JOURNAL, **68**, 2510 (1946).

[18] L. F. Fieser and R. G. Kennelly, *ibid.*, **57**, 1611 (1935)

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[19] The authors wish to express their gratitude to Miss C. Vitiello of the Schering Corp., Bloomfield, N. J., for obtaining the infrared absorption data and their interpretation.

[CONTRIBUTION FROM THE IPATIEFF HIGH PRESSURE AND CATALYTIC LABORATORY, DEPARTMENT OF CHEMISTRY, NORTHWESTERN UNIVERSITY]

Studies in the Terpene Series. XIX.[1] Hydroisomerization and Hydrogenolysis of Cyclohexene, Methylcyclohexene and *p*-Menthene in the Presence of Hydrogenation Catalysts

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The effect of hydrogen pressure and temperature was studied upon cyclohexene, 4-methylcyclohexene and *p*-menthene (1-methyl-4-isopropylcyclohexene) in the presence of a nickel–Kieselguhr catalyst. At lower pressures and higher temperatures the cyclohexenes undergo hydrogenation and hydrogenolysis accompanied by a skeletal isomerization. A similar reaction occurred when nickel–alumina or copper–alumina were used as catalysts.

The hydrogenolysis of pinane in a flow type apparatus in the presence of hydrogenation catalysts, such as nickel–Kieselguhr, nickel–alumina, copper–alumina and nickel, yielded tetramethylcyclohexanes, *o*- and *p*-menthane and a substantial amount of alkylcyclopentanes admixed with bicyclic dihydroterpenes.[5] The formation of the latter two types of compounds indicated that skeletal isomerization accompanied the hydrogenolysis of pinane. The formation of alkylcyclopentanes could have occurred through the isomerization of alkylcyclohexanes during the hydrogenolysis of pinane. In order to test this hypothesis the reactions of several monocyclic hydrocarbons were investigated under experimental conditions similar to those used in the study of the hydrogenolysis pinane. A more detailed study was made of cyclohexane since it was possible to determine the products of the reaction quantitatively by means of a mass spectrograph.

Experimental Results

1. Cyclohexene and Cyclohexane.—The experimental conditions and the composition of the product obtained from the interaction of cyclohexene and hydrogen over nickel–Kieselguhr catalyst are summarized in Table I. The extent of hydroisomerization decreases sharply with the increase of pressure (Fig. 1), and increases with the temperature of reaction (Fig. 2). The formation of cyclopentane most probably from methylcyclopentane, during hydrogenolysis is of interest in view of the work of Haensel and Ipatieff,[6,7] who found that a methyl group linked to a tertiary carbon atom is removed less readily than a methyl group on a secondary carbon. Thus the paraffins, namely, *n*-hexane and methylcyclopentanes found in the reaction product would be expected to lose a methyl

TABLE I

HYDROISOMERIZATION AND HYDROGENOLYSIS OF CYCLOHEXENE OVER NICKEL–KIESELGUHR CATALYST

The molal ratio of hydrogen to olefins used in the experiments was 4.5(±0.3):1. The hourly liquid space velocity (ml. liquid per hour per ml. catalyst) was 0.49(±0.05). The product withdrawn during the period of 1.5–3 hours was submitted for analysis. Values given in parentheses represent the composition of hydrogenolyzed and hydroisomerized product. They were calculated on benzene and cyclohexane free basis.

Experiment	1	2	3	4	5	6	7	8
Temp., °C.	235	265	293	268	230	275	293	262
Pressure, atm.	2	1.7	1.5	5.5	10.5	10.5	10	45.5
Product composition, mole %[a]								
Cyclohexane	95.8	88.5	73.1	96.0	99.1	98.2	97.4	99.8
Benzene	1.7	5.4	18.4	1.7	...	0.1	0.3	...
Cyclopentane	0.7(28)	1.6(26)	1.2(14)	0.4	...	.2	.2(9)	...
Methylcyclopentane	.6(24)	1.7(28)	2.2(26)	.8	.1	.7	.7(30)	...
n-Hexane	....	0.4(7)	0.5(6)	.1	.2	...	.6(26)	...
2-Methylpentane	.4(16)	0.6(10)	1.7(20)	.4	...	.1	.2(9)	...
3-Methylpentane	.5(20)	1.1(18)	1.5(18)	.5	.3	.5	.3(13)	0.1
2,3-Dimethylbutane	.3(12)	0.7(11)	1.0(12)	.1	.3	.2	.3(13)	.1

[a] Analyzed by means of a mass spectrograph.

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[1] For Paper XVIII of this series see H. Pines, E. F. Jenkins and V. N. Ipatieff, THIS JOURNAL, **75**, 6226 (1953).

[2] Universal Oil Products Company Predoctoral Fellow 1950–1952.

[3] On leave of absence from Société Chimique Rhône-Poulenc, Lyon, France.

[4] Deceased, November 29, 1952.

[5] V. N. Ipatieff, F. J. Pavlik and H. Pines, THIS JOURNAL, **75**, 5179 (1953).

[6] V. Haensel and V. N. Ipatieff, *ibid.*, **68**, 345 (1946).

[7] V. Haensel and V. N. Ipatieff, *Ind. Eng. Chem.*, **39**, 853 (1947).