151. *Experiments Relating to the Synthesis of Patulin. Part I. A Study of Hydrogenated γ-Pyrones.*

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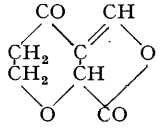
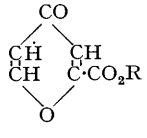
Tetrahydrocomanic acid has been prepared by catalytic hydrogenation of comanic acid and is identical with the acid $C_6H_8O_4$ obtained by hydrolysis of patulin by sulphuric acid. *Ethyl tetrahydrocomanate*, prepared by catalytic hydrogenation of ethyl comanate, has been condensed with ethyl orthoformate to yield ethyl 3- or 5-ethoxymethylenetetrahydrocomanate.

BIRKINSHAW, BRACKEN, MICHAEL, and RAISTRICK (*Lancet*, **1943**, ii, 625) have described the isolation of patulin from *Penicillium patulum* Bainier, and have advanced evidence consistent with the belief that patulin has formula (I) or is a tautomer or a mixture of tautomers thereof.

(I.) 

 (II.)

The experiments now described represent attempts to synthesise patulin by way of tetrahydro-γ-pyrones. The starting materials were comanic acid (II, R = H) and ethyl comanate (II, R = Et). Comanic acid was prepared by Haitinger and Lieben's method (*Monatsh.*, 1885, **6**, 279) of decarboxylation of monoethyl chelidonate, followed by hydrolysis. Monoethyl chelidonate was prepared in satisfactory yield by partial esterification of chelidonic acid with 5% alcoholic hydrogen chloride (for other methods of preparation, see Lerch, *Monatsh.*, 1884, **5**, 371; Haitinger and Lieben, *ibid.*, p. 342; Willstätter and Pummerer, *Ber.*, 1904, **37**, 3751; Dávila Núñez, *Rev. Acad. Cienc., Madrid*, 1932, **28**, 343; Lehmann, *Ber.*, 1935, **68**, 703). Its conversion into ethyl comanate presented no great practical difficulties. Hydrolysis to comanic acid was readily accomplished with boiling 2N-hydrochloric acid.

The catalytic hydrogenation of γ-pyrone and its derivatives has been studied by several authors (cf. Borsche, *Ber.*, 1915, **48**, 682; Mozingo and Adkins, *J. Amer. Chem. Soc.*, 1938, **60**, 669; Dávila Núñez, *loc. cit.*; *Anal. Soc. fís. quím.*, 1929, **27**, 637) and appears to be most selective with palladium catalysts either in the colloidal state (Borsche, *loc. cit.*; Cornubert and Robinet, *Bull. Soc. chim.*, 1933, **53**, 565) or supported on neutral materials (Cawley and Plant, J., 1938, 1214). Several types of palladium catalyst have been used in this work for the hydrogenation of different pyrone derivatives. A study of the absorption curves gave no evidence of selective hydrogenation, nearly 3 molecules of hydrogen being taken up in all instances, but by interrupting the reaction after the absorption of 1 or 2 mols. of hydrogen it was possible to isolate partially hydrogenated derivatives in poor yield. A number of experiments showed that no one catalyst was satisfactory in all cases and the results are summarised in the table.

Experiments on the hydrolysis of *ethyl tetrahydrocomanate* showed that, in boiling dilute solution, hydrolysis was complete at pH 2 in 3 hours and at pH 1 in 45 mins. Hydrolysis was very rapid with 0·1N-sodium hydroxide at room temperature, but with more concentrated alkali solution decomposition took place on heating.

Starting material.	Catalyst.	Conditions.*	Hydrogen uptake.	Product.	Properties.
Comanic acid	$Pd/BaSO_4$	Aqueous soln. R.T. and N.P.	6 atoms	Tetrahydro-γ-pyranol-2-carboxylic acid	M. p. 146—147°.
,,. ,,	,,	,, ,,	4 ,,	Tetrahydrocomanic acid (1)	M. p. 120°; semicarbazone, m. p. 188—189°; dinitrophenylhydrazone, m. p. 197°; *p*-phenylphenacyl ester, m. p. 139°.
,, ,,	,,	,, ,,	3 ,,	Dihydrocomanic acid (2)	M. p. 159—161°; ultraviolet absorption, see Fig. 1.
,, ,,	Pd/C	,, ,,	5 ,,	Tetrahydrocomanic acid	
Ethyl comanate	Pd colloidal	Aqueous alcoholic soln. R.T. and N.P.	5 ,,	Ethyl tetrahydrocomanate Ethyl tetrahydro-γ-pyranol-2-carboxylate	B. p. 84°/0·04 mm. B. p. 101—102°/0·04 mm.
Ethyl chelidonate	$Pd/BaSO_4$	Alcoholic soln. R. T. and N.P.	6 ,,	Ethyl tetrahydro-γ-pyranol-2 : 6-dicarboxylate Ethyl tetrahydrochelidonate	M. p. 48—50° M. p. 80—82°
,, ,,	Ni	Alcoholic soln. R.T. and N.P.	4 ,,	Ethyl dihydrochelidonate Ethyl tetrahydrochelidonate	M. p. 94°. M. p. 82—83°
Methyl chelidonate	,,	Methyl-alcoholic soln. R.T. and N.P.	4 ,,	Methyl dihydrochelidonate Methyl tetrahydrochelidonate	M. p. 181—182°; dinitrophenylhydrazone, m. p. 197—198°. M. p. 105—106°.
Chelidonic acid	$Pd/BaSO_4$	Aqueous soln.	6 ,,	Tetrahydro-γ-pyranol-2 : 6-dicarboxylic acid	M. p. 195—196°

(1) This proved to be identical with the acid $C_6H_8O_4$ obtained by the hydrolysis of patulin (Birkinshaw, Bracken, Michael, and Raistrick, *loc. cit.*), and we are indebted to the authors for comparing the two compounds and their derivatives. Tetrahydrocomanic acid exhibited an ultra-violet band of very low intensity ($\lambda_{max.}$ 2770 A., $\varepsilon_{max.}$ 12·8), which is consistent with a saturated ketone structure.

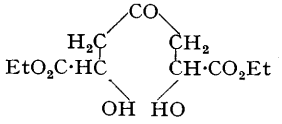
(2) This is believed to be 5 : 6-dihydrocomanic acid, since it is decarboxylated at the m. p., whereas the tetrahydro-acids are not. Satisfactory carbonyl derivatives were not obtained from this acid.

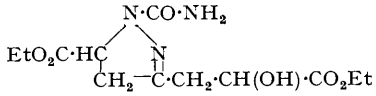
* R.T. and N.P. = room temperature and normal pressure.

Attempts were made to prepare the tetrahydro-compounds by complete reduction of chelidonic acid to *tetrahydro-γ-pyranol-2 : 6-dicarboxylic acid*, followed by oxidation of the secondary hydroxyl group. Oxidation of this acid and of its ethyl ester with nitric acid under a variety of conditions (cf. Mannich and Brose, *Ber.*, **1923**, **56**, 833) or with potassium permanganate or chromic acid failed to give ketonic compounds. Catalytic dehydrogenation with Raney nickel (cf. Paul, *Bull. Soc. chim.*, **1941**, **8**, 507) gave only a small amount of carbonyl compound, the bulk of the material remaining unchanged. Ketonic substances also were not obtained by oxidation with aluminium *iso*propoxide or aluminium *tert.*-butoxide in various solvents. Failure to oxidise tetrahydropyranols to tetrahydropyrones has been reported by Cornubert and Robinet (*Bull. Soc. chim.*, **1934**, **1**, 90).

In addition to the above methods of preparing tetrahydropyrones, their formation by the cyclisation of (III) was attempted (for a similar cyclisation, cf. Mannich and Brose, *loc. cit.*) :

(III.)





(IV.)

Ethyl αα'-dihydroxy-γ-ketopimelate (III) was readily prepared by the catalytic hydrogenation of acetonedioxalic ester and, though it possessed three active hydrogens as shown by the Zerewitinoff method, its ketonic nature was demonstrated by the formation of 3-(β-*carbethoxy*-β-*hydroxyethyl*)-5-*carbethoxy*-Δ^2-*pyrazoline*-1-*carboxyamide* (IV) on reaction with semicarbazide. Crystalline acetyl, benzoyl, and 3 : 5-dinitrobenzoyl derivatives of (III) could not be obtained.

Attempted cyclisation of the dihydroxy-ester by the method of Mannich and Brose (*loc. cit.*) led to extensive tar formation, and the use of hydrogen chloride in the cold in absence of a solvent (cf. Cornubert and Robinet, *loc. cit.*; *Compt. rend.*, **1932**, **194**, 1081) resulted in hydrolysis of the ester groups; although cyclisation of the required type was obtained, the product, tetrahydrochelidonic acid, was formed in very small yield.

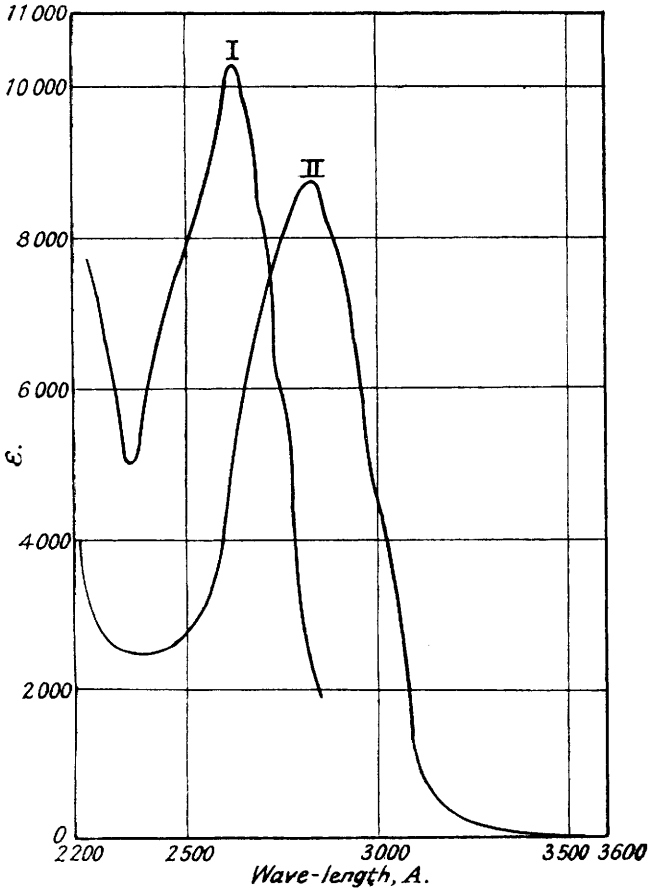
Treatment of the dihydroxy-ester with warm alcoholic hydrogen chloride did not effect cyclisation, but gave instead a chlorinated product, $C_{11}H_{16}O_5Cl_2$, which, although the structure has not been confirmed, is considered to be *ethyl αα'-dichloro-γ-ketopimelate*. When (III) was distilled in a vacuum over potassium bisulphate, two molecules of water were eliminated with the formation of ethyl 3-ketopentadiene-1 : 5-dicarboxylate (V, R = Et), which was identical with a specimen prepared by bromination of ethyl γ-ketopimelate, followed by dehydrobromination with quinoline (Strauss, *Ber.*, **1905**, **38**, 3296). This ester was hydrolysed by hot 2N-sulphuric acid to the corresponding acid (V, R = H), identical with the compound described by

Kommpa (*Ann. Acad. Sci. Fennicæ*, 1939, *A*, **51**, No. 3). This acid was also obtained by treatment of (III) with hot 2N-sulphuric acid.

(V.) $RO_2C{\cdot}CH{:}CH{\cdot}CO{\cdot}CH{:}CH{\cdot}CO_2R$

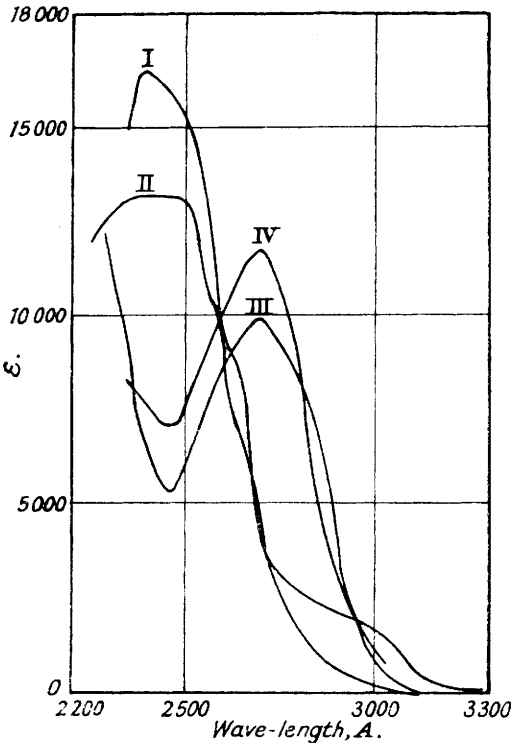
Thus (III) showed a pronounced tendency to pass into the conjugated straight-chain compound (V) and only a slight tendency towards cyclic ether formation. It may be that cyclic ether formation takes place readily only when phenyl or related groups are present (cf. Cornubert and Robinet, *loc. cit.*).

FIG. 1.



I. *Comanic Acid*, $\lambda_{max.}$ 2,600 A., ϵ 10,280.
II. *Dihydrocomanic Acid*, $\lambda_{max.}$ 2,820 A., ϵ 8,810.

FIG. 2.

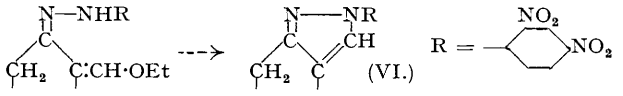


I. *Ethyl 3-Ketopentadiene-1 : 5-dicarboxylate*, $\lambda_{max.}$ 2,380 A., ϵ 16,600.
II. *3-Ketopentadiene-1 : 5-dicarboxylic Acid*, $\lambda_{max.}$ 2,400 A., ϵ 13,200.
III. *Ethyl Chelidonate*, $\lambda_{max.}$ 2,700 A., ϵ 10,000.
IV. *Chelidonic Acid*, $\lambda_{max.}$ 2,700 A., ϵ 11,800.
(Riegel and Reinhard, *J. Amer. Chem. Soc.*, 1926, **48**, 1341).

Compound (V, R = Et) bears a close structural relationship to ethyl chelidonate and in common with the latter it does not form a semicarbazone. On the other hand, the behaviour of the acid (V, R = H) and the ester (V, R = Et) on hydrogenation contrasts sharply with that of γ-pyrone derivatives. In (V, R = H and Et), the carbonyl group remained unattacked in presence of palladium-black catalyst and selective reduction of the double bonds took place to give γ-ketopimelic acid and its ethyl ester. The ultra-violet absorption spectra of (V, R = Et and H) compared with those of ethyl chelidonate and chelidonic acid are shown in Fig. 2.

Several attempts were made to introduce a substituent in the 3-position of the tetrahydropyrone nucleus. Claisen condensation of ethyl tetrahydrocomanate and tetrahydrochelidonate with ethyl formate and ethyl oxalate under a variety of conditions yielded mainly resins and the starting materials were themselves destroyed in the presence of sodium ethoxide. Condensation with formalin and paraformaldehyde, reaction with diphenylformamidine, and the Mannich base reaction with formaldehyde and diethylamine hydrochloride also yielded no useful product. Reaction, however, between ethyl tetrahydrocomanate, ethyl orthoformate, and acetic anhydride took place under vigorous conditions and at high temperatures to yield a substance, the analysis of which was correct for an *ethoxymethylenetetrahydrocomanic ester*. That the substance contains an ethoxymethylene group in the 3- or 5-position is indicated by its absorption spectrum ($\lambda_{max.}$ 2720 A., ε 12,800), which is consistent with the presence of an $\alpha\beta$-unsaturated ketone group and is similar to that of patulin

($\lambda_{max.}$ 2750 A., ε 15,800), and also by the formation of a 2 : 4-dinitrophenylhydrazone which, on standing in alcoholic sulphuric acid solution, cyclised to a *pyrazole* derivative (VI) :



Attempts to determine the position of the ethoxymethylene group by reaction with hydriodic acid after catalytic reduction (cf. Birkinshaw, Bracken, Michael, and Raistrick, *loc. cit.*) failed. Crystallographic data kindly supplied by Drs. D. Crowfoot and G. M. J. Schmidt were insufficient to decide whether the ethoxymethylene group was in position 3 or 5. The precise constitution of this compound has not, therefore, been fully determined.

It is realised that the present work is incomplete, but owing to pressure of other work this investigation has been abandoned.

Experimental.

The absorption spectra of the esters and of one acid (V; R = H) were measured in absolute alcohol, those of the other acids in water.

Monoethyl Chelidonate.—Chelidonic acid (300 g., dried at 100°) was refluxed with alcoholic hydrogen chloride (1500 c.c., 5%) for 3 hours, and the mixture then maintained at — 10° for 1 hour. The semi-solid mass was submitted to filtration (pump), and the solid well pressed. The filtrate was evaporated in a vacuum at 30—35° to small bulk (if the evaporation is carried out at higher temperatures, further esterification of the monoethyl chelidonate takes place), and more solid obtained from the pasty mass. The combined, moist solids were washed with ether and dried at 80°. Monoethyl chelidonate was obtained as a buff-coloured solid, m. p. 218—220° (183 g., yield 53%).

From the combined ethereal washings and final alcoholic filtrate, ethyl chelidonate was isolated by evaporation, solution of the residue in benzene, filtration through alumina, and addition of light petroleum (b. p. 40—60°) to the filtrate. It formed slightly coloured needles, m. p. 60—62° (89 g., yield 23%).

Other methods of preparing monoethyl chelidonate gave products which could not be decarboxylated as smoothly as the substance obtained as described above.

Ethyl Comanate.—When monoethyl chelidonate (150 g.) in a 1-l. flask connected through a long air-condenser to a water-pump was heated in an oil-bath to 230°, rapid decarboxylation took place and ethyl comanate distilled as a pale yellow liquid, which rapidly solidified. When the vigorous reaction had subsided, the bath temperature was raised to 260° until distillation ceased. Ethyl comanate, purified by redistillation (b. p. 161°/12 mm.) and then crystallisation from alcohol (distilled over Raney nickel), had m. p. 96—98° (103 g., yield 86·5%).

Decarboxylation of monoethyl chelidonate at ordinary pressure gave unsatisfactory results.

Comanic Acid.—Ethyl comanate (20 g.) was refluxed with 2N-hydrochloric acid (100 c.c.) for 1 hour. The hot solution was treated with charcoal and filtered. Comanic acid separated from the filtrate, on cooling, in slightly coloured needles, m. p. 253—254° after drying at 100° (15 g., yield 90%).

Hydrogenation of Comanic Acid.—(a) *Tetrahydro-γ-pyranol-2-carboxylic acid.* Comanic acid (0·7 g.) in water (50 c.c.) was shaken with hydrogen in presence of palladised barium sulphate (3·6% Pd, 0·7 g.) at room temperature and pressure. Hydrogenation was complete in 2 hours and approximately 3 molecules of hydrogen were absorbed. The catalyst was filtered off, and the filtrate evaporated to dryness in a vacuum. The residual syrup slowly crystallised to give tetrahydro-γ-pyranol-2-carboxylic acid, m. p. 146—147° after crystallisation from acetone. The compound was identical with the product prepared by the hydrolysis of the corresponding ester described below.

(b) *Tetrahydrocomanic acid.* Comanic acid (20 g.) in water (1400 c.c.) was hydrogenated as above in presence of palladised barium sulphate (20 g.), and the hydrogenation interrupted after absorption of 2 molecules of hydrogen. The catalyst was filtered off, and the filtrate evaporated to dryness in a vacuum. The residual syrup was thoroughly extracted with several portions of warm ether, the dried extracts evaporated, and the residue crystallised from chloroform (alcohol-free) and then from pure ethyl acetate to give small needles, m. p. 118—120° (2 g., yield 9·7%) (Found C, 50·1; H, 6·0. $C_6H_8O_4$ requires C, 50·0; H, 5·6%).

Comanic acid (9 g.) in water (630 c.c.) was hydrogenated as before in presence of palladised charcoal (10% Pd, 9 g.) Hydrogenation ceased after absorption of about 5 atoms of hydrogen. Isolation in the usual way gave 1 g. (yield 10·8%) of crude product, which, after two crystallisations from ether–light petroleum and further purification by Professor Raistrick and his colleagues, had m. p. 120°. A mixture of this compound with the acid $C_6H_8O_4$ (m. p. 121°) obtained by hydrolysis of patulin melted at 120·5°.

The p-*phenylphenacyl* ester, prepared by the method of Drake and Bronitsky (*J. Amer. Chem. Soc.*, 1930, **52**, 3716), had m. p. 139° (Found : C, 71·3; H, 5·6. $C_{20}H_{18}O_5$ requires C, 71·0; H, 5·4%). The mixed m. p. with the *p*-phenylphenacyl ester of the hydrolysis acid, $C_6H_8O_4$, from patulin (m. p. 139—140°) was 139·5°.

The *semicarbazone* was prepared by allowing a solution of tetrahydrocomanic acid (0·3 g.), semicarbazide hydrochloride (0·2 g.), and potassium acetate (0·2 g.) in water (5 c.c.) to stand in the cold for 24 hours. The crystalline precipitate formed clusters of colourless needles from hot water, m. p. 188—189° (decomp.) (Found : C, 42·1; H, 5·5; N, 20·5. $C_7H_{11}O_4N_3$ requires C, 41·8; H, 5·5; N, 20·9%).

The *dinitrophenylhydrazone* prepared from Brady's reagent was obtained as yellow orange needles from ethyl alcohol, m. p. 197°, not depressed by the dinitrophenylhydrazone of the $C_6H_8O_4$ acid from patulin (Found : N, 17·2. $C_{12}H_{12}O_7N_4$ requires N, 17·3%).

(c) *Dihydrocomanic acid.* Comanic acid (12·9 g.) in water (903 c.c.) was hydrogenated as above in the the presence of palladised barium sulphate (3·6% Pd, 12·9 g.), and the hydrogenation interrupted when 3 atoms of hydrogen had been absorbed. Isolation in the usual way yielded a semi-solid product which, crystallised from chloroform and then ethyl acetate, yielded flat prisms, m. p. 159—161° (decomp.) (1·9 g., yield 14·6%) (Found : C, 50·8; H, 4·6. $C_6H_6O_4$ requires C, 50·7; H, 4·3%).

Dihydrocomanic acid showed maximum absorption at 2820 A. (ε = 8,810) and absorbed two molecules of hydrogen on hydrogenation in presence of palladised barium sulphate.

Hydrogenation of Ethyl Comanate.—(a) *Ethyl tetrahydrocomanate.* A solution of ethyl comanate (125 g.) in a mixture of ethyl alcohol (distilled over Raney nickel; 625 c.c.) and water (625 c.c.), palladium chloride solution (2%; 30 c.c.), and gum acacia solution (1%; 60 c.c.) were mixed and shaken with hydrogen at room temperature and pressure. The hydrogenation ceased after absorption of about 5 atoms of hydrogen. The solution was then evaporated in a vacuum

at 35° to about 300 c.c., filtered, neutralised with saturated sodium bicarbonate solution, and continuously extracted with ether for 24 hours. The colloidal catalyst was coagulated by the ether and remained suspended in the aqueous layer. The dried ethereal extract yielded 100 g. of crude product, which was fractionated through a lagged column 45 cm. in length packed with single-turn glass helices and fitted with a return reflux still-head. The low-boiling fraction was rejected and *ethyl tetrahydrocomanate* distilled as a colourless liquid, b. p. 84°/0·04 mm., $n_D^{17°}$ 1·4609 (25 g., yield 19·5%) (Found : C, 55·4; H, 7·3. $C_8H_{12}O_4$ requires C, 55·8; H, 7·0%).

The structure of the ester was confirmed by hydrolysis. The ester (2 g.) was refluxed with 2N-sulphuric acid (20 c.c.) for 30 mins., cooled, neutralised with baryta (with rhodizonic acid as indicator), filtered, and the filtrate evaporated to dryness in a vacuum. The solid residue, m. p. 106—110° (1·6 g., yield 95%), of crude tetrahydrocomanic acid was crystallised from pure ethyl acetate and had m. p. 118—120° (Found : C, 49·9; H, 6·0%). The *p*-phenylphenacyl ester had m. p. 138° (Found : C, 70·6; H, 5·3%).

Tetrahydrocomanic acid (10 g.) was re-esterified by refluxing in ethyl alcohol (200 c.c.) with concentrated sulphuric acid (1·0 c.c.) for 1½ hours. The solvent was removed, and the residue poured into water and extracted with ether. The ethereal layer was washed with sodium bicarbonate solution, dried, and the solvent removed. Fractional distillation gave ethyl tetrahydrocomanate as a colourless liquid, b. p. 78°/0·05 mm., $n_D^{16°}$ 1·4610 (Found : C, 55·8; H, 7·0%).

(b) *Ethyl tetrahydro-γ-pyranol-2-carboxylate.* The high-boiling fraction in the distillation described above consisted of *ethyl tetrahydro-γ-pyranol-2-carboxylate*, b. p. 101—102°/0·04 mm., $n_D^{20°}$ 1·4647 (30 g., yield 23%) (Found : C, 55·9; H, 8·2; active H, 1·1. $C_8H_{14}O_4$ requires C, 55·2; H, 8·1%; active H, 1·0).

The structure of this ester was also confirmed by hydrolysis. The ester (2 g.) was refluxed for 3 hours with water (20 c.c.) containing a drop of 2N-sulphuric acid. The syrupy residue obtained on evaporation in a vacuum was crystallised from ethyl acetate and then from acetone to give *tetrahydro-γ-pyranol-2-carboxylic acid* in compact prisms, m. p. 145—146° (Found : C, 49·5; H, 7·2. $C_6H_{10}O_4$ requires C, 49·3; H, 6·9%). The p-*phenylphenacyl* ester had m. p. 155—156° (Found : C, 70·6; H, 6·2. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%).

Tetrahydro-γ-pyranol-2 : 6-dicarboxylic Acid.—Chelidonic acid (10 g.) in water (500 c.c.) was hydrogenated at ordinary temperature and pressure in presence of palladised barium sulphate (3·6%; 10 g.). Absorption of hydrogen ceased when 3 molecules had been taken up. The catalyst was filtered off, and the filtrate evaporated to dryness in a vacuum. The resulting viscous oil rapidly solidified to a crystalline mass (10 g., yield 97%), m. p. 181—183° (decomp.). Crystallisation from acetone–light petroleum (b. p. 60—80°) raised the m. p. to 195—196° (decomp.) (Found : C, 44·2; H, 5·6. $C_7H_{10}O_6$ requires C, 44·2; H, 5·3%).

Ethyl Tetrahydro-γ-pyranol-2 : 6-dicarboxylate.—Ethyl chelidonate (10 g.) in ethyl alcohol (200 c.c.) was hydrogenated at room temperature and pressure in presence of palladised barium sulphate (3·6%, 10 g.). Hydrogenation ceased when about 3 molecules of hydrogen had been absorbed. The catalyst was filtered off, and the alcohol removed from the filtrate by distillation in a vacuum. The resulting oil was distilled at 0·1 mm., two main fractions being collected : (*a*) b. p. 140—170°/0·1 mm., (*b*) 170—190°/0·1 mm.

Fraction (*b*) solidified partially on trituration with petrol and standing. The solid was collected and pressed as free as possible from oil. The solid (2·6 g., yield 25%) melted at 42—45°; crystallisation from ether–light petroleum (b. p. 40—60°) gave colourless needles of *ethyl tetrahydro-γ-pyranol-2 : 6-dicarboxylate*, m. p. 48—50° (Found : C, 54·3; H, 7·7; active H, 0·53. $C_{11}H_{18}O_6$ requires C, 53·6; H, 7·4%; active H, 1·0).

Fraction (*a*) also solidified partially on standing; the solid (0·8 g., yield 7·9%), freed from oil as above, crystallised from benzene–light petroleum (b. p. 40—60°) in white needles, m. p. 80—82°, not depressed by authentic ethyl tetrahydrochelidonate (Borsche, *loc. cit.*, gives m. p. 80—82°). Hydrolysis of this ester with boiling 2N-sulphuric acid, followed by continuous ether extraction, gave *tetrahydrochelidonic acid*, which crystallised from ethyl acetate in small cubes, m. p. 194—195° (Found : C, 44·9; H, 4·6. $C_7H_8O_6$ requires C, 44·7; H, 4·3%).

Ethyl tetrahydro-γ-pyranol-2 : 6-dicarboxylate was also prepared by esterification of the corresponding acid by means of ethyl-alcoholic hydrogen chloride. The product, isolated in the usual way, was an oil, which crystallised after trituration with light petroleum and cooling. Crystallisation from ether–petrol (b. p. 40—60°) gave colourless needles, m. p. 48—50°, alone or mixed with a specimen of the ester obtained as described above.

Hydrogenation of Ethyl Chelidonate with Raney Nickel as Catalyst.—Ethyl chelidonate (48 g.) in ethanol (100 c.c.) was hydrogenated at atmospheric pressure with Raney nickel catalyst (5 g.) until 2 molecules of hydrogen had been taken up (6 hours). The hydrogenation was then stopped, the catalyst separated, and the alcohol removed under reduced pressure below 40°. The residual oil with ether (20 c.c.) gave a sparingly soluble nickel salt (1·3 g.; m. p. *ca.* 140—150°) which afforded *ethyl dihydrochelidonate* on treatment with warm 4N-hydrochloric acid. The latter crystallised from benzene in almost colourless prismatic needles, m. p. 94° (Found : C, 55·0; H, 5·9. $C_{11}H_{14}O_6$ requires C, 54·6; H, 5·8%). It gave a clear red colour with alcoholic ferric chloride.

Vacuum distillation of the residual oil after separation of the nickel salt led to much decomposition and a poor yield. It was found better, first to cool at 0° before distillation and isolate the crystalline ethyl tetrahydrochelidonate which separated, the yellow oil being washed out with cold ether. The ethereal washings were then evaporated and distilled. Decomposition still occurred and only about half the material distilled at *ca.* 160—200°/2—4 mm., a considerable dark viscous residue remaining (collection of various fractions gave no improved yield). The distillate gave crystals on cooling which were separated as before. The total yield averaged 15—18% of the theoretical, m. p. *ca.* 73—80°. Recrystallisation from ether gave pure ethyl tetrahydrochelidonate, m. p. 82—83° (Found : C, 54·0; H, 6·3. Calc. for $C_{11}H_{16}O_6$: C, 54·1; H, 6·6%).

Hydrogenation of Methyl Chelidonate.—Methyl chelidonate was conveniently prepared from ethyl chelidonate. The latter was dissolved in methanol (4 parts) containing potassium acetate (1 equiv.) or sodium methoxide (catalytic amounts). Facile alcoholysis occurred and methyl chelidonate crystallised in 90% yield, m. p. 122°. We are indebted to Dr. A. Koebner for this observation.

Reduction was carried out as for the ethyl ester, the methyl ester (8·5 g.) in methanol (125 c.c.) and Raney nickel (2 g.) being used. The reduction product was chilled with methanol (5 c.c.) and afforded 0·25 g. of a nickel salt (m. p. 144—150°) which, on treatment with warm dilute hydrochloric acid, gave a nickel-free substance crystallising from ethyl acetate in needles, m. p. 177—178°, shown by mixed m. p. to be identical with the methyl dihydrochelidonate described below.

The residue after removal of the nickel salt distilled without decomposition and the distillate (6 g.; b. p. 165—171°/1 mm.) crystallised readily. Trituration with ether gave 2·5 g. of colourless solid, m. p. 96—136°, not raised by recrystallisation from benzene–light petroleum. Extraction with methanol left an insoluble residue (0·17 g.; m. p. 170—180°). Crystallisation of this from benzene and from ethyl acetate gave *methyl dihydrochelidonate* as colourless needles, m. p. 181—182° (decomp.) after sintering at 178° (Found : C, 50·2; H, 4·7. $C_9H_{10}O_6$ requires C, 50·5; H, 4·7%). It was strongly enolic, giving a red coloration with alcoholic ferric chloride. It was soluble in warm, aqueous sodium bicarbonate and was precipitated unchanged on acidification (recovery *ca.* 30%). It formed a *dinitrophenylhydrazone*, m. p. 197—198° (Found : C, 46·5; H, 3·9. $C_{15}H_{14}O_9N_4$ requires C, 45·7; H, 3·55%). When hydrogenated

in presence of Raney nickel, the uptake was 90% of that required for the absorption of 4 atoms of hydrogen, but no crystalline product could be isolated apart from a small amount of nickel salt.

The methanolic extract above on evaporation gave *methyl tetrahydrochelidonate*, which crystallised from benzene–light petroleum in almost colourless prisms, m. p. 104—105° (1·7 g.). Recrystallisation from benzene raised the m. p. to 105—106° (Found: C, 50·1; H, 5·9. $C_9H_{12}O_6$ requires C, 50·0; H, 5·6%). In subsequent reductions it was obtained in 24% yield and was more readily isolated than the corresponding ethyl ester.

Ethyl αα′-Dihydroxy-γ-ketopimelate.—Acetonedioxalic ester (175 g.) was hydrogenated in ethyl acetate solution (1 l.) in presence of palladised barium sulphate (3·6% Pd; 60 g.). Absorption of hydrogen ceased after 20 hrs. when 2·5 molecules of hydrogen had been absorbed. The solution was filtered and dried over ignited sodium sulphate, and the ethyl acetate removed in a vacuum. The crude product was distilled and the main fraction (85 g.; yield 49%), b. p. 173—181°/0·5 mm. with slight decomp., was purified by redistillation. The product was a pale yellow liquid, b. p. 140—141°/0·09 mm., $n_D^{20.7°}$ 1·4688 (Found: C, 50·25; H, 7·4; active H, 2·87. $C_{11}H_{18}O_7$ requires C, 50·4; H, 6·9%; active H, 2·0).

Hydrogenation can be accomplished in 10 hrs. with palladised charcoal (10% Pd) to give the same yield of product, but it was found necessary to wash the charcoal thoroughly with hot 10% hydrochloric acid before preparation of the catalyst. Raney nickel was ineffective as a catalyst, for its activity was quickly destroyed by an alcoholic solution of acetonedioxalic ester. Attempted hydrogenation of the disodium enolate of acetonedioxalic ester in alcoholic suspension in the presence of Raney nickel was also unsuccessful.

3-(β-Carbethoxy-β-hydroxyethyl)-5-carbethoxy-Δ²-pyrazoline-1-carboxyamide.—An aqueous solution (15 c.c.) of ethyl αα′-dihydroxy-γ-ketopimelate (0·5 g.) was warmed (40°) and shaken with semicarbazide hydrochloride (0·2 g.) and anhydrous sodium acetate (0·2 g.). The colourless crystalline precipitate was recrystallised from alcohol, forming colourless plates, m. p. 152° (Found: C, 47·8; H, 6·35; N, 13·95; OEt, 31·1. $C_{12}H_{19}O_6N_3$ requires C, 47·8; H, 6·35; N, 13·9; OEt, 28·9%). When a few mg. were dissolved in concentrated sulphuric acid and a few drops of sodium nitrite solution added, a pale blue colour characteristic of pyrazolines (Knorr, *Ber.*, 1893, **26**, 100) developed.

Ethyl 3-Ketopentadiene-1 : 5-dicarboxylate.—Ethyl αα′-dihydroxy-γ-ketopimelate (27 g.) was refluxed in a vacuum (bath at 150°) for 10 minutes with fused potassium hydrogen sulphate (2 g.) and then distilled. Ethyl 3-ketopentadiene-1 : 5-dicarboxylate distilled as a bright yellow liquid which readily solidified in the receiver. The crude product (15 g.) formed bright yellow needles from ether (12 g.; yield 52%), m. p. 49—50°, and retained its bright yellow colour after repeated treatment with charcoal. Strauss (*loc. cit.*) gives m. p. 49·5—50° and a mixture with a specimen prepared by his method melted at 49—50° (Found: C, 58·25; H, 6·2. Calc. for $C_{11}H_{14}O_5$: C, 58·4; H, 6·2%).

3-Ketopentadiene-1 : 5-dicarboxylic Acid.—Ethyl αα′-dihydroxy-γ-ketopimelate (10 g.) was refluxed with 2N-sulphuric acid (50 c.c.) for 2 hrs. On cooling, fine yellow crystalline flakes were obtained (yield 4 g.; 53%) which on recrystallisation from alcohol had m. p. 236° (decomp.) (Found: C, 49·6; H, 3·8; equiv., 85. Calc. for $C_7H_8O_5$: C, 49·4; H, 3·6%; equiv., 86). Kommpa (*loc. cit.*) gives m. p. 230° for this compound. A specimen of the acid prepared by hydrolysis of the ethyl ester with 2N-sulphuric acid had m. p. 233° (decomp.), mixed m. p. 233° (decomp.). The acid was reconverted into the ester, m. p. and mixed m. p. 49—50°, by esterification with ethyl alcohol by an azeotropic method.

Ethyl αα′-Dichloro-γ-ketopimelate.—Dry hydrogen chloride was passed into a warm solution of ethyl αα′-dihydroxy-γ-ketopimelate (6 g.) in ethanol (20 c.c.) until saturated. On cooling and standing, a crystalline solid was deposited (2 g.; yield 29%) which, on recrystallisation from light petroleum, formed colourless needles, m. p. 74° (Found: C, 44·0; H, 5·4; Cl, 24·2. $C_{11}H_{16}O_5Cl_2$ requires C, 44·2; H, 5·4; Cl, 23·7%). The *ester* gave a positive ketonic reaction with 2 : 4-dinitrophenylhydrazine in alcoholic sulphuric acid solution.

Hydrogenation of Ethyl 3-Ketopentadiene-1 : 5-dicarboxylate and of γ-Ketopentadienedicarboxylic Acid.—The ester (3·0 g.) was hydrogenated in ethyl acetate solution (15 c.c.) in presence of palladium-black (0·02 g.). Hydrogenation ceased after absorption of 2 molecules of hydrogen. The solution was filtered and the ethyl acetate removed, leaving a colourless liquid, which was hydrolysed with boiling 2N-sulphuric acid (25 c.c.). By continuous extraction with ether, γ-ketopimelic acid (1·2 g.; yield 51%) was isolated; on recrystallisation from acetone and sublimation at 120°/0·02 mm. it had m. p. 140° (Found: C, 48·25; H, 5·9. Calc. for $C_7H_{10}O_5$: C, 48·3; H, 5·8%). It was identical with an authentic specimen of γ-ketopimelic acid, m. p. 141·5°, prepared by the method of Kommpa (*loc. cit.*). The *semicarbazone* was prepared in aqueous solution and on recrystallisation from water formed colourless needles, m. p. 183—184° (decomp.) (Found: C, 41·35; H, 5·7; N, 18·1. $C_8H_{13}O_5N_3$ requires C, 41·6; H, 5·7; N, 18·2%). The semicarbazone prepared from an authentic specimen of γ-ketopimelic acid had m. p. 184° (decomp.) and a mixture of the two had m. p. 183—184° (decomp.) (Found: C, 41·65; H, 5·7; N, 17·9%). γ-Ketopentadienedicarboxylic acid was hydrogenated in presence of palladium-black in ethanol solution and yielded γ-ketopimelic acid, m. p. 140—141°.

Tetrahydrochelidonic Acid.—Ethyl αα′-dihydroxy-γ-ketopimelate (10 g.) was saturated at room temperature with dry hydrogen chloride and after 3 days the mixture was dissolved in ether and extracted with saturated sodium bicarbonate solution (100 c.c.). The aqueous extract was acidified and by continuous extraction with ether a small quantity of brown oil was obtained, which partially crystallised on standing. The crystalline material was washed with ether and recrystallised from ethyl acetate, m. p. 188°. A mixture with authentic tetrahydrochelidonic acid (m. p. 194°) melted at 188°. The yield was too small for analysis.

Ethyl Ethoxymethylenetetrahydrocomanate.—A mixture of ethyl tetrahydrocomanate (4·6 g.), ethyl orthoformate (20 g.), and acetic anhydride (26 c.c.) was heated in a sealed tube at 190—200° for about 16 hrs. The products from three such reactions were combined, volatile substances removed by vacuum distillation, and the residue distilled at 0·05 mm. Unchanged tetrahydrocomanic ester (8·5 g.) was collected up to 100°. The fraction boiling between 100° and 130° (3·9 g.) partially solidified on standing; the solid was collected, pressed free from oil, and recrystallised from ether. *Ethyl ethoxymethylenetetrahydrocomanate* was obtained in long colourless needles (1 g., yield 13·8%, based on tetrahydrocomanic ester consumed), m. p. 79—81° (Found: C, 58·15; H, 7·25; OEt, 38·8. $C_{11}H_{16}O_5$ requires C, 57·9; H, 7·1; OEt, 39·5%). The compound showed maximum absorption at 2720 A. ($\epsilon = 12{,}800$). A solution of the compound in alcohol developed a deep red colour fairly rapidly on treatment with ferric chloride solution.

Treatment of the compound (0·2 g.) in ethyl alcohol (10 c.c.) with a solution of 2 : 4-dinitrophenylhydrazine (0·2 g.) in ethyl alcohol (20 c.c.) containing concentrated sulphuric acid (3·0 c.c.) caused the rapid precipitation of a dark red solid. This was collected after 15 minutes and crystallised from alcohol, giving the 2 : 4-*dinitrophenylhydrazone* of ethoxymethylenetetrahydrocomanic ester as small red crystals, m. p. 168—170° (Found: C, 49·8; H, 5·1. $C_{17}H_{20}O_8N_4$ requires C, 50·0; H, 4·9%).

If the reaction mixture was allowed to stand overnight, the red solid redissolved and addition of 2N-sulphuric acid to the point of precipitation, followed by cooling, gave a yellow solid, which, after crystallisation from ethyl alcohol, melted at 141—142°. The compound gave no colour with alcoholic potassium hydroxide, showing that it was not a 2 : 4-dinitrophenylhydrazone, and the analysis indicated that it was *ethyl* 1-(2″ : 4″-*dinitrophenyl*)-3 : 4-*pyrazolo*-3′ : 4′ *tetrahydropyrane*-2′(6′)-*carboxylate* (Found: C, 49·3; H, 4·0; N, 15·4. $C_{15}H_{14}O_7N_4$ requires C, 49·7; H, 3·9; N, 15·5%).

Microanalyses were carried out by Miss H. King and Mr. S. Bance.

The authors wish to thank Miss M. A. Smith and Miss A. J. Radnor for assistance in the preparation of intermediates.

The authors, engaged in the laboratories of member-companies of the Therapeutic Research Corporation, London, have carried out the work described in this and the following paper under the auspices of the Corporation.

THERAPEUTIC RESEARCH CORPORATION OF GREAT BRITAIN LTD.,
LONDON, W.C.2.

[*Received, September 25th*, 1944.]