105. *The Rearrangement of Furfuryl Alcohol to Methyl Lævulate.*

By K. G. Lewis.

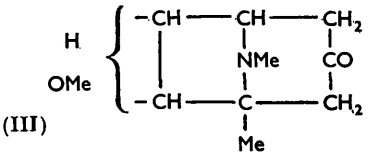
The structure of the substance isolated originally by Pummerer and Gump [1] from the rearrangement of furfuryl alcohol by methanolic hydrogen chloride, has been determined. A number of closely related substances has been shown to rearrange to methyl lævulate. A mechanism for this rearrangement is suggested.

Pummerer and co-workers [1,2] isolated from the mixture obtained by treatment of furfuryl alcohol with methanolic hydrogen chloride a substance ($C_8H_{16}O_4$) to which they assigned the structure δ-methoxylævulaldehyde dimethyl acetal (I). They showed [1] that treatment of this substance with acid gave methyl lævulate in good yield, and claimed that it was an essential intermediate in the formation of methyl lævulate from furfuryl alcohol. Deriaz, Stacey, Teece, and Wiggins [3] repeated this work, and accepted the structure of the intermediate as (I) and prepared from it a bis-2 : 4-dinitrophenylhydrazone (II), m. p. 221° (Pummerer *et al.*[2] recorded 192°). Clauson-Kaas [4] synthesised a δ-methoxylævulaldehyde bis-2 : 4-dinitrophenylhydrazone, m. p. 248°, and drew attention to the discrepancy in the recorded melting points. Marked differences also exist in the properties of synthetic

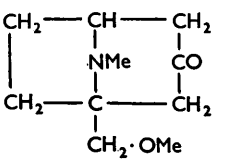
[1] Pummerer and Gump, *Ber.*, 1923, **56**, 999.
[2] Pummerer, Guyot, and Birkofer, *Ber.*, 1935, **68**, 480.
[3] Deriaz, Stacey, Teece, and Wiggins, *J.*, 1949, 1222.
[4] Clauson-Kaas, *Acta Chem. Scand.*, 1952, **6**, 556.

δ-methoxylævulaldehyde dimethyl acetal (I) and the product isolated by Pummerer *et al.*[1,2] and Deriaz *et al.*[3] The synthetic acetal is, moreover, not rearranged by acids. Subsequently, Clauson-Kaas and Nielsen [5] showed that the furfuryl alcohol intermediate ($C_8H_{16}O_4$) could be converted into a methoxy-tropinone (III) which was different from the methoxy-tropinone (IV) derived from authentic δ-methoxylævulaldehyde by a similar reaction sequence. Clauson-Kaas *et al.*[5] deduced that the structure of the intermediate ($C_8H_{16}O_4$) was (α or β)-methoxylævulaldehyde dimethyl acetal (V) or (VI).

$MeO{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CH(OMe)_2$ (I)



(III)



(IV)

(V) $Me{\cdot}CO{\cdot}CH_2{\cdot}CH(OMe){\cdot}CH(OMe)_2$ $Me{\cdot}CO{\cdot}CH(OMe){\cdot}CH_2{\cdot}CH(OMe)_2$ (VI)

Similar conclusions, based on different evidence, had been reached independently in these laboratories. It was found that the bis-2 : 4-dinitrophenylhydrazone (II) prepared as described by Deriaz *et al.*[3] contained, in addition to a methoxy-group, a *C*-methyl group. The original substance ($C_8H_{16}O_4$) gave a positive iodoform reaction, and, when treated with 2 : 4-dinitrophenylhydrazine in hot methanolic acid, formed 4-oxopent-2-enal bis-2 : 4-dinitrophenylhydrazone (VII). The above evidence indicates that the substance ($C_8H_{16}O_4$) must be either (V) or (VI). It was then subjected to the haloform reaction in the expectation that the reaction would produce either of two methoxy-acids, determination of the structures of which would decide between (V) and (VI). When the substance ($C_8H_{16}O_4$) was treated with sodium hypochlorite, dichloroacetic acid and a neutral liquid ($C_6H_{12}O_3Cl_2$) were isolated. The latter contained three methoxyl groups, and, when treated with 2 : 4-dinitrophenylhydrazine under the correct conditions, formed a mono-derivative, which still contained a methoxyl group and two chlorine atoms. If three methoxyl groups are present in the neutral liquid, then, assuming the remaining carbon atoms form a nucleus, relatively few formulations are possible, the conditions of the haloform reaction being considered. Thus structures possessing a chlorine atom and a methoxyl group attached to the same carbon atom may be discarded, as the halogen atom would be highly reactive and very easily hydrolysed in aqueous solution. Three structures (VIII—X) must be considered.

$CHCl_2{\cdot}CH(OMe){\cdot}CH(OMe)_2$ (VIII) $MeO{\cdot}CH_2{\cdot}CCl_2{\cdot}CH(OMe)_2$ (IX) $CHCl_2{\cdot}C(OMe)_2{\cdot}CH_2{\cdot}OMe$ (X)

The isolation of the derivative of 4-oxopent-2-enal (VII) indicates (cf. ref. 5) the skeleton Me·CO·C·C·CHO for the original, and thus eliminates the ketal structure (X). Of the two remaining possibilities, only (VIII) agrees with the facts. Consideration of a possible mechanism for the anomalous haloform reaction supports this assignment. Formulæ (V) and (VI) for the original substance ($C_8H_{16}O_4$) correspond to the two structures (VIII) and (IX) for the haloform product. The two tetrachloro-substituted precursors required by a haloform reaction yielding dichloroacetic acid and substance (VIII) or (IX) would have structures (XI) and (XII), respectively.

(XI) $CHCl_2{\cdot}CO{\cdot}CCl_2{\cdot}CH(OMe){\cdot}CH(OMe)_2$ $CHCl_2{\cdot}CO{\cdot}CH(OMe){\cdot}CCl_2{\cdot}CH(OMe)_2$ (XII)

Substitution on the " wrong " side in haloform reactions has been observed as a side reaction, together with normal substitution, even in simple aliphatic ketones.[6] In the

[5] Clauson-Kaas and Nielsen, *Acta. Chem. Scand.*, 1955, **9**, 475.
[6] Cullis and Hashmi, *J.*, 1956, 2512.

halogenation of compound (V), reaction presumably occurs first on the side away from the methyl group, where the hydrogen atoms are activated by the inductive electron withdrawal of the methoxy-group. When both of these hydrogen atoms are replaced, substitution of the hydrogen atoms of the methyl group occurs, and abnormal fission of the molecule takes place after four chlorine atoms have been introduced. Similar fission across the " wrong " C–C bond has been observed by Cullis and Hashmi [6] during iodoform reaction of methyl *iso*propyl ketone, where the formation of *iso*propyl iodide and iodoacetic acid was shown to occur in addition to the normal products. These authors suggest that premature fission of the haloform product before complete substitution of the hydrogens of the methyl group is favoured by steric hindrance, and the intermediate (XI), or its anion, would presumably be considerably hindered. (The formation of some chloroform and normal C–C bond fission is not excluded, as the original substance does give an iodoform test.)

The formation from structure (VI) of the tetrachlorinated intermediate (XII) would seem most improbable. Halogenation adjacent to the acetal grouping by sodium hypochlorite is unusual, but that the hydrogen atom on the methoxyl side should remain unsubstituted under these conditions is even more improbable. On the basis of the considerably greater enolic content of methoxyacetone [7] than that of acetone, it would be expected that substitution would occur first on the side of the methoxyl group. Fission at the stage of substitution (XII) would also seem less likely than for (XI).

This evidence favours structure (VIII) for the neutral haloform product and thus α-methoxylævulaldehyde dimethyl acetal (V) for the product isolated from the rearrangement of furfuryl alcohol. Formulation (V) is in good agreement with the following: (i) The ready formation of the bis-2 : 4-dinitrophenylhydrazone (VII) from (V) in hot

(XIII) $Me\cdot CO\cdot CH{:}CH\cdot CH(OMe)_2 + MeOH \rightleftharpoons$ (V)

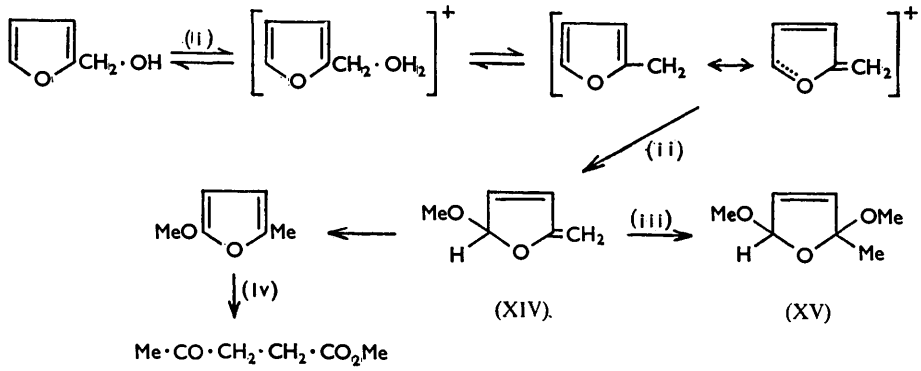
methanolic hydrochloric acid. (ii) The occurrence together in the mixture from the treatment of furfuryl alcohol with methanolic benzenesulphonic acid of 4-oxopent-2-enal dimethyl acetal (XIII) and the methoxy-acetal (V). The conversion (XIII) ⟶ (V) should be governed by the free carbonyl group, and thus yield the α-methoxy-isomer. Conversely, if the unsaturated acetal were formed from compound (V), elimination of the methoxy-group, under the mildly acidic conditions, should occur from the carbon atom β to the free carbonyl group.[8] (iii) The stability of the rearrangement product (V) to both Fehling's solution and ammoniacal silver nitrate at room temperature. It is reported that α-methoxy-ketones [such as (VI)] have powerful reducing properties, in particular that Fehling's solution [9, 10] and ammoniacal silver nitrate [9, 11] are rapidly reduced in the cold.

The mechanism of conversion of furfuryl alcohol into lævulic acid, by aqueous acids, has been discussed recently by Dunlop and Peters,[12] and, as modified for methanol solution, is as shown on page 534 (first set of formulæ).

These authors discounted the structure δ-methoxylævulaldehyde dimethyl acetal for the product isolated by Pummerer and co-workers [1, 2] and, to account for the observed ease of conversion into methyl lævulate, suggested that it was probably one of the formulæ (XVI—XVIII), which, they suggested, could be formed from the intermediate (XIV) by addition of methanol to give (XV). This, by rearrangement and addition of methanol with or without ring opening, would yield (XVI), (XVII), or (XVIII). The present work

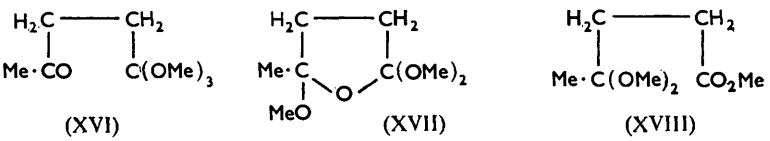
[7] Kenner and Richards, *J.*, 1953, 2240.
[8] Houben-Weyl, " Methoden der organischen Chemie" (Sauerstoff-verbindungen, 11), G. Thieme, Stuttgart, 4th. Edn., Vol. VII, pt. 1, p. 384.
[9] Leonardi and de Franchis, *Gazzetta*, 1903, **33**, 319.
[10] Henry, *Rec. Trav. chim.*, 1904, **23**, 343.
[11] Gauthier, *Ann. Chim. Phys.*, 1909, **16**, 319.
[12] Dunlop and Peters, " The Furans," Reinhold Publ. Co., New York, 1953, p. 646.

establishes the identity of Pummerer's intermediate as α-methoxylævulaldehyde dimethyl acetal, and the ready rearrangement of this substance to methyl lævulate, observed by previous workers [1,3] and confirmed in this work, remains to be explained.



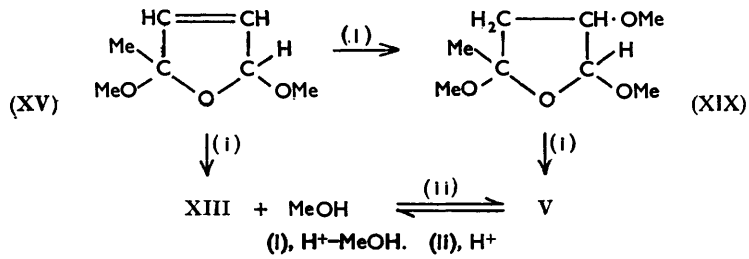
(i), H^+. (ii), MeOH. (iii), H^+–MeOH. (iv), H^+–MeOH–H_2O.

The mixture obtained when furfuryl alcohol is heated with methanolic acid is quite complex, and the following compounds, in addition to methyl lævulate, have been isolated, either in this work (indicated [a]) or by Clauson-Kaas *et al.*—furfuryl methyl ether [a], tetrahydro-2 : 4 : 5-trimethoxysylvan[5,a], 4-oxopent-2-enal dimethyl acetal[a], methyl lævulate



ketal,[5] and α-methoxylævulaldehyde dimethyl acetal [5,a]. All these compounds on further treatment with methanolic hydrogen chloride are converted into methyl lævulate. In addition, it has been observed in this work and by Clauson-Kaas *et al.*[5] that 2 : 5-dimethoxy-2 : 5-dihydrosylvan (XV) is similarly converted into methyl lævulate.

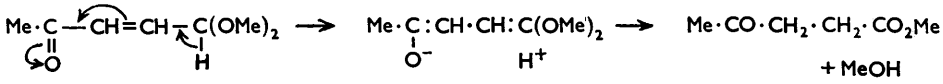
The transformation of methyl lævulate ketal into the ester requires no comment. The other four compounds may be inter-related as follows :



(I), H^+–MeOH. (II), H^+

The dihydrosylvan (XV) was not isolated from the fractionation of the rearrangement mixture, although a search for it was made. It is believed that the products (V), (XIII), and (XIX) are formed as outlined above from the dihydrosylvan (XV), and that this is formed from furfuryl alcohol, essentially as already indicated.[12] The essential intermediate in the rearrangement of the above compounds to methyl lævulate is considered to be the unsaturated acetal (XIII), into which, in the presence of methanolic hydrogen chloride,

they may all be converted. The mechanism suggested for the transformation of the acetal (XIII) into methyl lævulate may be represented as follows :



(XIII) (XX)

Extended enolisation of the carbonyl group results in the loss of the hydrogen atom attached to the carbon of the potential aldehyde group. The intermediate (XX) is then of ketone acetal type, and would undergo addition and elimination as indicated. Under absolutely anhydrous conditions, the addition of methanol with the formation of some orthoester might be expected. However, in the furfuryl alcohol rearrangement water is produced so that conditions are such that the normal ester and not the orthoester would be expected.

The suggested mechanism involving the unsaturated acetal (XIII) is similar to one proposed by Isbell [13] to explain one stage of the conversion of 2-deoxypentoses into lævulic acid.

Experimental

δ-Methoxylævulaldehyde Dimethyl Acetal (I).—(i) *Methyl tetrahydro-2 : 5-dimethoxyfurfuryl ether.* This compound, prepared independently by a sequence of reactions similar to those of Clauson-Kaas,[4] had b. p. 86°/14 mm., $n^{15.5}$ 1·4325 (Found : C, 54·8; H, 9·1. Calc. for $C_8H_{16}O_4$: C, 54·5; H, 9·15%) (Clauson-Kaas [4] records b. p. 81—82°/12 mm., n^{25} 1·4285). The bis-2 : 4-dinitrophenylhydrazone of δ-methoxylævulaldehyde had m. p. 242° (decomp.) (from nitrobenzene) (Found : C, 44·4; H, 3·7; N, 22·5; OMe, 6·4. Calc. for $C_{18}H_{18}O_9N_8$: C, 44·1; H, 3·7; N, 22·9; OMe, 6·3%) (lit.,[4] m. p. 248°). (ii) *δ-Methoxylævulaldehyde dimethyl acetal.* The tetrahydrofuran derivative (21 g.) was added to dry methanol (80 ml.) containing hydrogen chloride (2 g.) and the mixture set aside for 4 days at 15° and then for 4 days at 30° (conditions used by Hall and Howe [14] for the ring opening of 2 : 6-diethoxytetrahydropyran). The solution was made just alkaline by the addition of methanolic sodium methoxide, and carbon dioxide was bubbled through the solution to neutralise excess of alkali. The solution was filtered, the solvent evaporated, and the residue fractionated in a vacuum. Three fractions were collected. Fraction (1) (6 g.), b. p. 86—87°/15 mm., $n^{19.5}$ 1·4307, was unchanged starting material; fraction (2), intermediate; fraction (3) (12 g.), b. p. 119—120°/15 mm., n^{19} 1·4312, was *δ-methoxylævulaldehyde dimethyl acetal* (Found : C, 54·5; H, 9·15; OMe, 51·2. $C_8H_{16}O_4$ requires C, 54·5; H, 9·15; 3OMe, 52·8%). For α-methoxylævulaldehyde dimethyl acetal isolated from the rearrangement of furfuryl alcohol, Pummerer *et al.*[2] record b. p. 100—101°/16 mm.; Deriaz *et al.*[3] b. p. 89—90°(bath)/6 mm., n^{18} 1·4236; Clauson-Kaas *et al.*[5] b. p. 112/21 mm., n^{25} 1·4229. The bis-2 : 4-dinitrophenylhydrazone formed from fraction (3) had m. p. 240° (decomp.) (from nitrobenzene) undepressed on admixture with the δ-methoxylævulaldehyde bis-2 : 4-dinitrophenylhydrazone described above (Found : C, 44·5; H, 3·9; OMe, 5·9%). There was a marked depression on admixture with α-methoxylævulaldehyde bis-2 : 4-dinitrophenylhydrazone. Treatment of δ-methoxylævulaldehyde with aqueous or methanolic acid did not yield either lævulic acid or methyl lævulate.

α-Methoxylævulaldehyde Dimethyl Acetal (V).—A solution of furfuryl alcohol (100 g.) in methanol (1 l.) containing hydrogen chloride (1 g.) was refluxed for 4 hr.[1,3] Excess of anhydrous potassium carbonate was then added, the methanol distilled off, and the mixture filtered and rapidly distilled in a vacuum. The distillate, b. p. 40—110°/11 mm., was fractionated directly, the sodium hydrogen sulphite separation used by previous workers [2,3] being omitted. *α-Methoxylævulaldehyde dimethyl acetal* had b. p. 92°/9 mm., 105°/17 mm., n^{18} 1·4262 (Found : C, 55·0; H, 9·2; O, 36·3; OMe, 47·9, 51·8. $C_8H_{16}O_4$ requires C, 54·5; H, 9·15; O, 36·3; 3OMe, 52·8%).

Reaction of the Methoxy-acetal (V) *with* 2 : 4-*Dinitrophenylhydrazine.*—(i) *In methanol.* The methoxyacetal was added to a boiling 1% solution of 2 : 4-dinitrophenylhydrazine in 1% methanolic hydrochloric acid. After some time, the hot methanolic solution was filtered and

[13] Isbell, *J. Res. Nat. Bur. Stand.*, 1944, **32**, 45.
[14] Hall and Howe, *J.*, 1951, 2480.

the residue washed with hot methanol. The residue was crystallised from nitrobenzene–tetrachloroethane to give 4-oxopent-2-enal bis-2 : 4-dinitrophenylhydrazone, m. p. 267° (decomp.) (Found : C, 44·9; H, 3·3; N, 24·6. Calc. for $C_{17}H_{14}O_8N_8$: C, 44·5; H, 3·1; N, 24·45%). There was no m. p. depression on admixture with authentic material, and the substance showed the ultraviolet absorption characteristic of this system.[15] From the hot methanolic filtrate and washings, there was obtained on cooling methyl lævulate 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 141—142°. (ii) *In water.* The methoxy-acetal (V) was added to a warm (30°) 1% solution of 2 : 4-dinitrophenylhydrazine in aqueous sulphuric acid (10% by volume). (conditions of Pummerer *et al.*[2]). The orange powder that separated was filtered off, and washed thoroughly with water, dried, and recrystallised from ethyl acetate; it had m. p. 220° (Deriaz *et al.*[3] record m. p. 221°) (Found : C, 44·6; H, 3·7; N, 22·7; OMe, 6·1; *C*-Me, 2·0. Calc. for $C_{18}H_{18}O_9N_8$: C, 44·1; H, 3·7; N, 22·9; OMe, 6·3; 1 *C*-Me, 3·1%).

Haloform Reaction on α-Methoxylævulaldehyde Dimethyl Acetal.—The methoxy-acetal (V) (30 g.) was added to a solution of sodium hypochlorite, prepared by passing the theoretical quantity of chlorine (53 g.) into ice-cold sodium hydroxide (62 g.) solution. After the solution had been maintained at *ca.* 50° for 1 hr., it was cooled and extracted with methylene chloride. The extract was dried ($MgSO_4$), the solvent evaporated, and the residue distilled to yield 3 : 3-*dichloro-2-methoxypropanal dimethyl acetal* (VIII) (18·5 g., 53%), b. p. 99°/18 mm., n^{22} 1·4450 (Found : C, 35·8, 35·4; H, 6·05, 6·0; Cl, 35·0; OMe, 44·7, 44·3. $C_6H_{12}O_3Cl_2$ requires C, 35·5; H, 5·9; Cl, 35·0; 3OMe, 45·8%). The alkaline solution left after the methylene chloride extraction was acidified; the resultant solution on continuous extraction with ether yielded dichloroacetic acid, b. p. 97—99°/19 mm., n^{23} 1·4618 (lit., 102°/20 mm., n^{20} 1·4658). The amide, m. p. 96—98°, anilide, m. p. 116—117°, and benzylamide,[16] m. p. 96—97°, formed from the above acid were undepressed on admixture with the corresponding authentic derivatives of dichloroacetic acid.

3 : 3-*Dichloro-2-methoxypropanal* 2 : 4-*Dinitrophenylhydrazone.*—Treatment of the chloro-acetal (VIII) with 2 : 4-dinitrophenylhydrazine (1%) in aqueous sulphuric acid (10% by vol.) (to which some methanol was added to assist solution of the starting material) yielded an orange solid. After chromatography on alumina and crystallisation from methanol the 2 : 4-*dinitrophenylhydrazone* formed yellow plates, m. p. 125—126·5° (Found : C, 36·4; H, 3·3; N, 16·5; Cl, 20·4; OMe, 8·8. $C_{10}H_{10}O_5N_4Cl_2$ requires C, 35·6; H, 3·0; N, 16·6; Cl, 21·0; OMe, 9·2%).

Identification of 4-*Oxopent-2-enal Dimethyl Acetal* (XIII).—The unsaturated acetal was isolated by fractionation of the mixture obtained from the rearrangement of furfuryl alcohol in methanol containing benzenesulphonic acid. Concentration of acid and other conditions were similar to those used for the rearrangement by hydrogen chloride. 4-*Oxopent-2-enal dimethyl acetal* had b. p. 83°/9 mm., n^{18} 1·4460, $\lambda_{max.}$ 223 and 315 mμ (log ε 3·83 and 1·53, respectively) in 95% ethanol (Found : C, 58·2; H, 8·3; OMe, 42·1. $C_7H_{12}O_3$ requires C, 58·3; H, 8·4; 2OMe, 43·0%). The structure was confirmed by hydrogenation to lævulaldehyde dimethyl acetal. The unsaturated acetal (XIII) was hydrogenated in methanol, 5% palladium–barium sulphate catalyst being used. Hydrogenation ceased after the rapid uptake of 1 mol. of hydrogen. After evaporation of the solvent and distillation there was obtained lævulaldehyde dimethyl acetal, b. p. 91—92°/19 mm., n^{19} 1·4193 (lit.,[17] b. p. 87—88°/17 mm.) (Found : C, 57·5; H, 9·9; OMe, 40·5. Calc. for $C_7H_{14}O_3$: C, 57·6; H, 9·65; 2OMe, 42·5%). Lævulaldehyde dimethyl acetal formed a characteristic bis-2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 236—237° (from nitromethane) (Found : N, 24·5. Calc. for $C_{17}H_{16}O_8N_8$: N, 24·3%) (lit.,[18] m. p. 235·5—236·5°), and (with phenylhydrazine) dihydromethylphenylpyridazine, m. p. 196—197° (from alcohol) (Found : N, 16·4. Calc. for $C_{11}H_{12}N_2$: N, 16·3%) (lit.,[17] m. p. 197°). The authentic specimen of lævulaldehyde bis-2 : 4-dinitrophenylhydrazone was prepared [19] by the treatment of sylvan at room temperature with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid; it had m. p. 236—237° (Found : N, 24·1%).

Rearrangement of the Compounds (V), (XIII), *and* (XV) *by Hydrogen Chloride.*—The compound (0·5 g.) was dissolved in methanol (50 ml.) containing hydrogen chloride (1·25 g.), and

[15] Lewis, *J.*, 1956, 1083.
[16] Buehler and Mackenzie, *J. Amer. Chem. Soc.*, 1937, **59**, 421.
[17] Harries, *Ber.*, 1898, **31**, 37.
[18] Strain, *J. Amer. Chem. Soc.*, 1935, **57**, 758.
[19] Wilson, *ibid.*, 1948, **70**, 1315.

the solution refluxed for 1 hr. and then poured into a methanolic solution of 2 : 4-dinitrophenylhydrazine (0·7 g.) containing 1% of hydrochloric acid. The solid formed on cooling was filtered off and washed thrice with methanol. After chromatography over alumina, elution with benzene, and crystallisation from methanol, the methyl lævulate 2 : 4-dinitrophenylhydrazone had m. p. and mixed m. p. 141—142°. The yield of dinitrophenylhydrazone was 70—75%.

The microanalyses were carried out by Dr. K. W. Zimmermann of the C.S.I.R.O. Microanalytical Laboratory, Melbourne. The author thanks Dr. N. V. Riggs and Mr. V. R. Stimson (University of New England) and Dr. P. de Mayo (University of Glasgow) for much helpful discussion.

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