[Contribution from the Chemical Laboratory of Northwestern University]

THE BROMINATION OF LEVULINIC ACID

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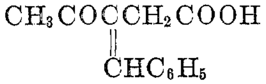
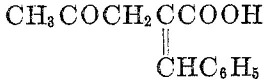
Levulinic acid is an unusual compound in the sense that each of its three methylene groups is situated next to a carbonyl group. In some of its reactions, as with benzaldehyde for example, substitution may be controlled so as to enter any of the three positions. 5-Benzylidenelevulinic acid (I) is formed in the presence of hot, dilute alkali (1, 2); 3-benzylidenelevulinic acid (II) in the presence of sodium acetate (3); and 2-benzylidenelevulinic acid (III) in the presence of ammonia or amines (4).

I $C_6H_5CH{=}CHCOCH_2CH_2COOH$

II



$$CH_3CO\underset{\underset{CHC_6H_5}{\|}}{C}CH_2COOH$$



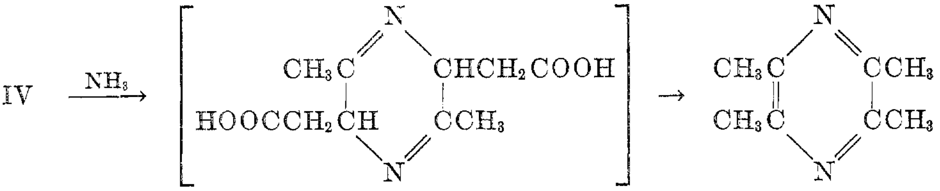
$$CH_3COCH_2\underset{\underset{CHC_6H_5}{\|}}{C}COOH$$

III

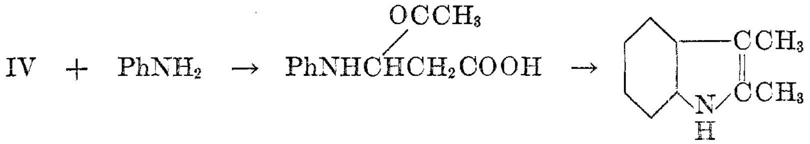
Halogenation of aliphatic compounds is generally influenced by carbonyl groups but conditions apparently have not been found for synthesis of all three bromolevulinic acids on direct bromination.

Bromination in conc'd hydrochloric acid solution yields 3-bromolevulinic acid (IV). Neither Wolff (5) who prepared it first (m.p. 59°) nor later workers (6, 7) ever reported a yield. Hughes and Watson's best melting point (7) was 56°. In support of the structure this acid was found to change into acetylacrylic acid, $CH_3COCH{=}CHCOOH$, on reaction with sodium hydroxide or sodium acetate (5), and to give rise to tetramethylpyrazine if heated at 110–120° with ammonia:

$$CH_3COCHBrCH_2COOH \qquad IV$$



That IV will react with aniline (5, 8) at 100° to yield 2,3-dimethylindole also supports the structure, since 4-methylquinoline should have been formed from 2-bromolevulinic acid.



Wolff prepared 2-bromolevulinic acid, m.p. 79–80°, by treating acetylacrylic acid with hydrogen bromide, again without stating yields but he did mention that a trace of IV was formed also.

The 2,3- and 3,5-dibromolevulinic acids are known. The former, m.p. 107–108°, was formed by addition of bromine to acetylacrylic acid (5), and the latter, m.p. 114–115°, was obtained in 85% yield by bromination of levulinic acid in ether (9) or chloroform (10). Tribromolevulinic acid, also obtained in this reaction, melts at 82°.

In the present work it was established that much of the difficulty in purifying 3-bromolevulinic acid according to Wolff's procedure could be avoided by fractional vacuum distillation (to eliminate the dibromo compound) rather than crystallization.

The Hell-Volhard-Zelinsky method was studied also. Bromination of levulinic acid with one mole of bromine in the presence of 0.016 gram-atom of phosphorus gave rise to 3,5-dibromolevulinic acid as the chief product. Larger quantities of phosphorus promoted formation of tar. Since only a small amount of IV was ever isolated, this is evidence that IV brominated at a faster rate than levulinic acid itself. It is interesting to note that bromination attacked positions 3 and 5 rather than 2. Simple aliphatic acids always brominate at position 2 in the Hell-Volhard-Zelinsky procedure.

Additional evidence for the accepted structure of the 3,5-dibromo acid was obtained in the present work. When it was treated with sodium hypochlorite in the haloform reaction, the product obtained was bromodichloromethane, not chloroform. Since this dibromo acid was obtained by bromination of 3-bromolevulinic acid it establishes the structure of the dibromo acid as the 3,5-compound.

The sodium salt of either the 3-bromo or the 3,5-dibromo acids did not precipitate on adding a sodium ethoxide solution to a solution of the acids in ether. Use of a large excess of ether and dioxane caused the separation either of acid salts or of mixtures of salt and acid. Analyses indicated variable compositions. Salts of β-bromo acids are known to decompose as follows: $RCHBrCH_2COONa \rightarrow RCH{=}CH_2 + NaBr + CO_2$, but no evidence for any spontaneous decomposition of this type was observed in these experiments.

EXPERIMENTAL

3-Bromolevulinic acid. In Wolff's procedure (5), 4 parts of bromine was added dropwise at 0° to 3 parts of levulinic acid and 12 parts of conc'd hydrochloric acid. In the final processing the oil was left to crystallize in a vacuum desiccator over sulfuric acid. We found that this operation usually failed to induce solidification but did cause a large loss. In six hours, for example, a 5-g. sample of the oil lost 1.2 g. or 20%. The recommended procedure is the following.

Into a stirred, cooled (0° to 5°), mixture of 50 g. of levulinic acid and 165 g. of conc'd hydrochloric acid was added 70 g. of bromine dropwise during one to two hours. White crystals of 3,5-dibromolevulinic acid separated. The mixture was stirred at 0–5° for two additional hours and then was poured into ice-water. The white solid was collected. It (7.3 g., m.p. 102–103°) melted at 113–114° after several recrystallizations from a mixture of carbon disulfide and benzene (1:1). The filtrate was then extracted with 100 ml. of anhydrous ether. The ether was distilled and 42.5 g. of a yellow oil was obtained.

The oil was distilled at 0.6 mm. and 125–130° to yield 32 g. of distillate, a colorless liquid which formed a crystalline mass when chilled at −10° for 24 hours; m.p. 47–50°. Two recrystallizations from carbon disulfide (5 g. of solvent to 1 g. of solid) raised the m.p. to 55–56°. From the 6 g. of distillation residue was obtained 2.2 g. of 3,5-dibromolevulinic acid, m.p. 110.5–111.5°, by crystallization from a mixture of carbon disulfide and benzene.

Separation of a mixture of mono- and di-bromolevulinic acids. A mixture consisting of 63% 3-bromolevulinic acid and 37% 3,5-dibromolevulinic acid was dissolved in carbon disulfide. After all solvent was removed, the oily residue set to a solid mass, m.p. 40–44°; Br, 48.0%.

To separate this, 8.5 g. of the mixture was distilled from a modified Claisen flask at 87° and 0.1 mm.; yield, 5.7 g.; m.p. 49–51° after chilling to solidify it. One crystallization from carbon disulfide gave m.p. 54–57°; Br, 41.4 (Calc'd: Br, 41.0 for $C_5H_7BrO_3$).

Extraction of the non-volatile portion with ether yielded 2 g. of white solid, m.p. 78–88°. One crystallization from benzene gave m.p. 110.5–111.5°; Br, 57.5 (Calc'd: Br, 58.3 for $C_5H_6Br_2O_3$).

Bromination with two moles of bromine in the presence of phosphorus. To 29 g. of levulinic acid was added 0.5 g. of red phosphorus. Then 80 g. of bromine was added dropwise with stirring. The mixture was stirred and was kept at 15° for 4.5 hours, then was poured into ice-water, filtered, and dried. A total of 38 g. of white solid was obtained, m.p. 90–100°. After three recrystallizations from carbon disulfide and benzene (1:1) the solid melted at 112.5–113°. A mixture melting point with 3,5-dibromolevulinic acid (m.p. 113–114°) was 113–114°.

From the filtrate, by extraction with 50 ml. of anhydrous ether, was obtained 20.3 g. of a yellow oil. After ten days at −10° there resulted 18.4 g. of crystals, m.p. 75–85°, from which 3,5-dibromolevulinic acid, m.p. 110–111° was obtained. A total of 54.5 g. (79.5%) of this dibromo acid was formed.

About 0.5 g. of 3-bromolevulinic acid, m.p. 52–53°, was separated from the 4 g. of oily filtrates.

Bromination with one mole of bromine in the presence of phosphorus. These conditions were employed: 58 g. of levulinic acid, 0.5 g. of red phosphorus, 80 g. of bromine, 4-hours duration at 15° as before. From the 82.5 g. of brown oily product 29 g. of the 3,5-dibromo acid (m.p. 112.5–113.5° after two crystallizations) separated after several days at −10° even though it was seeded with 3-bromolevulinic acid crystals.

Vacuum-distillation (0.08 mm. and 75–100°) of the 53.5 g. of oily filtrate yielded 22.7 g. of distillate. Only one-third of this could be made to crystallize by chilling or using solvents and chilling. These crystals melted at 51–52°, indicating 3-bromolevulinic acid. From the non-volatile portion 7–8 g. of the dibromo acid, m.p. 111–112.5°, was separated from an equal weight of tarry product.

Haloform reaction. To 5 g. of 3,5-dibromolevulinic acid, m.p. 113–114°, was added dropwise 75 ml. of cold "Chlorox" solution (5% sodium hypochlorite). A sweet odor could be detected and a green-yellow liquid separated at the bottom of the flask. The liquid was steam-distilled; yield, 2.3 g. (80%) of a yellow-green liquid. It was dried over calcium chloride and then distilled; b.p. 91.5°, n_D^{15} 1.5007, d_4^{15} 1.93. These constants agree with those of bromodichloromethane.

Reaction of 3,5-dibromolevulinic acid and sodium ethoxide. A sodium ethoxide solution (20 ml.) containing 0.14 g. of sodium was added to 2 g. of 3,5-dibromolevulinic acid in 70 ml. of ether and 30 ml. of dioxane at 0–3°. No carbon dioxide was liberated. White crystals (pink tint) separated which were collected and dried; yield, 1.14 g. This material reacted to tests as follows:

(a) *Anal.* Na, 3.94, 4.47, and 5.73 on separate runs.

(b) Water-soluble, solution reacting acid to litmus.

(c) Treatment of 0.1341 g. of the solid (3.94% Na) in 50 ml. of distilled water with 3 ml. of nitric acid (1:1) and 1.25 ml. of 0.1 *N* silver nitrate yielded 0.0150 g. of silver bromide. Ether extraction of the filtrate gave 0.10 g. of 3,5-dibromolevulinic acid, m.p. and mixture m.p. 110–111°.

(d) Ether extraction of 0.10 g. of the solid (4.47% Na) yielded 0.03 g. of 3,5-dibromolevulinic acid in the solution and 0.07 g. of an insoluble material of 10.11% Na content.

(e) A solution of 0.30 g. of the solid (5.73% Na) in 0.5 g. of distilled water was mixed with 10 ml. of alcohol, then 10 ml. of ether and 10 ml. of dioxane at 0°. About 0.1 g. of yellow-white solid of 14.49% Na content separated.

These are the calculated values for sodium: $C_5H_5Br_2NaO_3$, 7.77; $C_5H_5Br_2NaO_3 \cdot C_5H_6Br_2O_3$, 4.03; NaBr, 22.3.

3-Bromolevulinic acid and sodium ethoxide. Sodium ethoxide solution (10 ml., 0.07 g. of sodium) was stirred into a solution of 1 g. of 3-bromolevulinic acid and 20 ml. of ether at 0°. It was necessary to add 15 ml. of dioxane and 75 ml. of ether to cause the separation of 0.03 g. of cream-colored solid (Na, 8.60%). Calc'd for Na: $C_5H_6BrNaO_3$, 10.6; $C_5H_6BrNaO_3 \cdot C_5H_7BrO_3$, 5.58.

SUMMARY

Experiments are recorded on the syntheses and reactions of 3-bromolevulinic acid and 3,5-dibromolevulinic acid.

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