Orientation Studies in the Coumaran Series. Revised Structure of the Nitration Product of 5-Acetamido-2-methylcoumaran *via* the Elucidation of the Claisen Rearrangement of *m*-Acetoamidophenyl Allyl Ether

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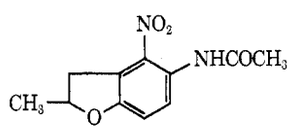
Arnold and McCool[1] reported that 2-methyl-5-acetamidocoumaran, on nitration, gave 2-methyl-4-nitro-5-acetamidocoumaran (**1**). This orientation appeared somewhat surprising since the above authors reported that the nitration of 2-methyl-4-acetamidoanisole yielded the 5-nitro isomer.[1]



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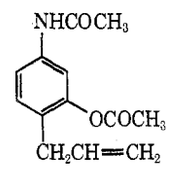

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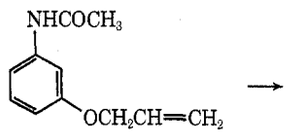
We now give evidence that the orientation in the two series is quite comparable and that the nitro coumaran obtained by Arnold and McCool was, in fact, the 6-nitro isomer.

The structure **1** assigned by Arnold, *et al.*,[1] to the nitration product of 2-methyl-5-acetamidocoumaran was based on the following considerations: (1) formation of a steam-volatile nitrophenol obtained from the nitration product by a Sandmeyer reaction; (2) conversion of the nitration product, by hydrolysis → deamination → reduction → acetylation, into an acetamido compound (mp 96–97°) different from 2-methyl-6-acetamidocoumaran (mp 126–126.5°) prepared by the cyclization of 3-acetoxy-4-allyl-acetanilide (**2**).[2]

The correctness of the last piece of evidence is, of course, based on the unquestionability of the structure of **2**. In our hands, following the method as described by Arnold, McCool, and Schultz[2] for the synthesis of **2**, the thermal rearrangement (Claisen reaction)[3] of *m*-acetamidophenyl allyl ether (**3**) yielded the two isomers (**4** and **5**) we expected from this type of reaction.[4]

The structures **4** and **5**, we respectively assigned to the two isomers, were supported by uv, ir, and nmr analyses and by conversion of **5** into the known 2-propyl-5-acetamidophenol.[2] It is probable that the product (mp 132–133°) obtained by Arnold, *et al.*,[2] and assumed by these authors to be 3-acetoxy-4-allylacetanilide (**2**) was in fact a mixture of the two isomers **4** and **5**. Consequently, on cyclizing the product (mp 132–133°) the above authors would have obtained both



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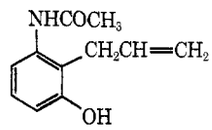
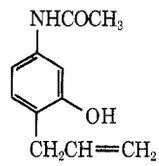
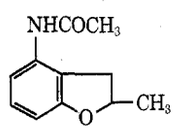


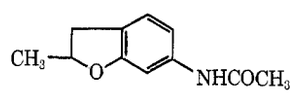
4, mp 155–157°



5, mp 162–164°



6, mp 121–123°

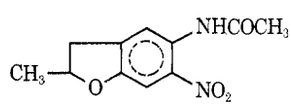


7, mp 99–101°

4- and 6-acetamidocoumarans. From this mixture they isolated only the higher melting isomer **6**, to which they assigned structure **7**.

We have cyclized the compounds **4** and **5**, respectively, to the corresponding acetamidocoumarans (**6** and **7**); the one derived from **5** was proved to be identical with the acetamidomethylcoumaran obtained by deamination and reduction of the nitroacetamidomethylcoumaran prepared by Arnold and McCool.[1]

In conclusion, the correct structure of the nitration product of 2-methyl-5-acetamidocoumaran must be **8**, which is also consistent with uv, ir, and nmr spectra.[5]



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Experimental Section[6]

Thermal Rearrangement of *m*-Acetamidophenyl Allyl Ether (3).—This reaction was carried out according to the directions of Arnold, McCool, and Schultz.[2] The solid, mp 129–132°, by thin layer chromatography revealed the presence of two spots and was treated as follows in order to separate the two isomers.

2-Allyl-3-hydroxyacetanilide (4).—The rearranged product of **3** (35 g) was dissolved in 150 ml of hot AcOEt. The solution was allowed to stand at room temperature overnight. The crystalline precipitate was separated from the supernatant (L_1) and dissolved in 200 ml of boiling AcOEt. The white crystals separated from the cooled solution (L_2) were collected, washed with cold AcOEt, and dried, 10.4 g, mp 155–157°. An analytical sample was recrystallized from AcOEt: mp 155–157°;[7] uv max 278 mμ (ε 2450); ir, a strong peak at 13.1 μ (characteristic of three adjacent aromatic C–H bonds); nmr (Me_2SO) 6.5–7.25 ppm (complex, 3-H phenyl); tlc, one spot (R_f 0.35). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.27; H, 6.86; N, 7.24.

(1) R. T. Arnold and J. C. McCool, *J. Amer. Chem. Soc.*, **64**, 1315 (1942).

(2) R. T. Arnold, J. C. McCool, and E. Schultz, *ibid.*, **64**, 1023 (1942).

(3) For a detailed study of the Claisen reaction see, for instance, K. Schmid, W. Haegale, and H. Schmid, *Helv. Chim. Acta*, **37**, 1080 (1954).

(4) Analogously, K. D. Kaufman and W. E. Russey [*J. Org. Chem.*, **30**, 1320 (1965)] reported the isolation of 2-allyl- and 4-allylresorcinol in the thermal rearrangement of resorcinol monoallyl ether.

(5) Nmr ($CDCl_3$) δ 2.72 (m, H_3), 3.22 (m, H_3'), 4.85 (m, H_2), 5.59 (t, H_4), 7.3 ppm (s, H_7), $J_{H_3,4}$ = 1.5, $J_{H_4,7}$ = 0.0 Hz.

(6) *Melting points were taken in capillary tubes in a heated copper block* and are corrected. Ultraviolet spectra were determined on a Cary Model 15 spectrophotometer in 95% EtOH. Infrared spectra were recorded on a Perkin-Elmer 157 spectrophotometer in KBr pellets. Nmr spectra were recorded on a Varian A-60A instrument. Thin layer chromatography was carried out on silica gel plates using chloroform, concentrated ammonia, and methanol (95:0.25:5) as developing solvent system.

(7) Arnold, *et al.*,[2] assigned to this compound mp 160.5–162°. Probably, from the mixture of the two isomers they isolated the 4 isomer, which they assumed to be the 2 isomer.

3-Hydroxy-4-allylacetanilide (5).—The solutions L_1 and L_2 (see above) were combined and the resulting solution was evaporated under reduced pressure to dryness. The residue (22.5 g, mp 124–139°) was suspended in 500 ml of H_2O. The suspension was heated to the boiling point; EtOH was gradually added until a clear solution was obtained.

The solution was heated for a further 15 min and allowed to stand at room temperature overnight. The crystalline solid was filtered and dried, 15.2 g, mp 161–163°. An analytical sample was recrystallized from an EtOH–H_2O mixture: mp 162–164°; uv max 247 mμ (ε 13,600), 285 (4570); ir, a strong peak at 12.1 μ (characteristic of two adjacent aromatic C–H bonds) and at 11.4 μ (characteristic of an isolated aromatic C–H bond); nmr (Me_2SO) δ 6.9 (s, $H_{5,6}$), 7.3 ppm (s, H_2); tlc, one spot (R_f 0.25). *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.38; H, 6.93; N, 7.23.

2-Allyl-3-acetoxyacetanilide.—A solution of 1.3 ml of AcCl in 15 ml of anhydrous PhH was added dropwise and with stirring to a cooled (10°) mixture of 2 g of 4 and 1.5 ml of pyridine in 85 ml of anhydrous PhH. After the addition was completed, the reaction mixture was stirred for an additional 2 hr and then filtered. The filtrate was shaken with H_2O, $NaHCO_3$ solution and again with H_2O until neutral. The PhH solution was dried (Na_2SO_4) and evaporated. The residue was crystallized from AcOEt to constant melting point (151–152°), tlc one spot (R_f 0.45). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.94; H, 6.42; N, 5.90.

3-Acetoxy-4-allylacetanilide.—This compound was prepared by a procedure similar to the one used for the 2-allyl isomer. After crystallization from PhH–petroleum ether (bp 30–60°), it melted at 103–104°, uv max 246 mμ (ε 18,500), tlc one spot (R_f 0.35). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.98; H, 6.42; N, 6.17.

2-Propyl-3-hydroxyacetanilide.—An ethanolic solution of 1.74 g of 4 in 25 ml of EtOH was hydrogenated under 3 atm in the presence of 0.15 g of PtO_2. After 3 hr the reaction mixture was filtered and the filtrate was evaporated to dryness. The residue (1.5 g, mp 163–165°) was crystallized twice from an EtOH–H_2O mixture: mp 167–169°; uv max 278 mμ (ε 2280); tlc one spot (R_f 0.20). *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.39; H, 7.82; N, 7.25. Found: C, 68.51; H, 7.84; N, 7.32.

3-Hydroxy-4-propylacetanilide.—This compound was prepared following the above procedure from 5. After recrystallization from an EtOH–H_2O mixture it melted at 173–175° (lit.[2] mp 173–174.5°): uv max 248 mμ (ε 12,800), 285 (4550); tlc one spot (R_f 0.25). *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.39; H, 7.82; N, 7.25. Found: C, 68.26; H, 7.78; N, 7.32.

2-Methyl-4-acetamidocoumaran (6).—Two grams of 2-allyl-3-hydroxyacetanilide was cyclized by means of fuming hydrobromic acid according to Arnold and McCool.[1] The obtained solid (1.7 g) was crystallized from PhH–petroleum ether to constant melting point (121–123°[8]): uv max 237 mμ (ε 8600), 283 (2550); tlc one spot (R_f 0.55). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.25; H, 6.83; N, 7.25.

2-Methyl-6-acetamidocoumaran (7).—This compound was obtained from 5 using the above procedure. After crystallization from PhH–petroleum ether, it had mp 99–101° and was identical (mixture melting point determination, ir and uv analyses) to the acetamidomethylcoumaran derived from the nitro compound prepared as described by Arnold and McCool:[1] uv max 249 mμ (ε 10,200), 291 (5780); tlc one spot (R_f 0.35). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.99; H, 7.02; N, 7.45.

Registry No.—**3**, 37439-78-4; **4**, 37439-79-5; **4** acetate, 37439-80-8; **5**, 28583-69-9; **5** acetate, 37439-82-0; **6**, 37439-83-1; **7**, 37439-84-2; 2-propyl-3-hydroxyacetanilide, 37439-85-3; 3-hydroxy-4-propylacetanilide, 28583-72-4.

Acknowledgment.—We are indebted to Miss A. De Leonibus for the microanalyses and to Mrs. M. L. Reviglio Lembo for the tlc data and uv and ir spectra.

(8) This compound was identified previously[1] as 2-methyl-6-acetamidocoumaran, mp 126–126.5° (from water).

An Alternate Synthesis of 5-Thio-D-glucose Pentaacetate[1]

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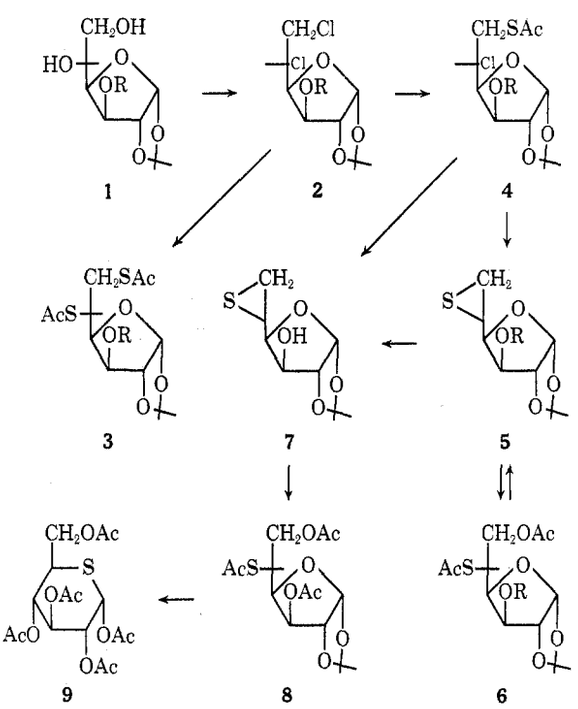
Because of growing interest in the biochemistry of 5-thio-D-glucose,[2] a shorter route to its synthesis would be highly desirable. It occurred to us that, since chloro sugars have proved valuable intermediates in the preparation of deoxy[3,4] and amino sugars,[5–7] they might be used to provide a shorter synthesis of 5-thio-D-glucose.

We find that 3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (1) can be easily chlorinated to produce 3-*O*-benzoyl-5,6-dichloro-5,6-dideoxy-β-L-idofuranose (2) in 72% yield, by using triphenylphosphine in carbon tetrachloride.[8] The L-ido configuration of compound 2 is established through its conversion to 5,6-dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose (7).[9]



Selective displacement of the primary chloro group on 2 produces 6-*S*-acetyl-5-chloro-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-idofuranose (4) in 60% yield if 1 mol of potassium thioacetate is used at low tempera-

(1) This work was supported by Public Health Service Research Grant No. AM 15641. Journal Paper No. 4861 of the Purdue Agricultural Experiment Station, Lafayette, Indiana 47907.

(2) R. L. Whistler and W. C. Lake, *Biochem. J.*, in press.

(3) M. F. Evans, L. Long, Jr., and F. W. Parrish, *J. Org. Chem.*, **33**, 1074 (1968).

(4) B. T. Lawton, D. J. Ward, W. A. Szarek, and J. K. N. Jones, *Can. J. Chem.*, **47**, 2899 (1969).

(5) S. Hanessian and N. R. Plessas, *Chem. Commun.*, 1152 (1967).

(6) B. T. Lawton, W. A. Szarek, and J. K. N. Jones, *ibid.*, 787 (1969).

(7) E. Hardeggar, G. Sanetti, and K. Steiner, *Helv. Chim. Acta*, **46**, 282 (1963).

(8) J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966).

(9) L. D. Hall, L. Hough, and R. A. Pritchard, *J. Chem. Soc.*, 1537 (1961).