Anisole-2,3,5,6-tetracarboxylic Acid Methyl Ester

The crude anisole-2,3,5,6-tetracarboxylic acid (2 mg) was dissolved in 1 ml of methanol. The solution was methylated with ethereal diazomethane for 30 min. The methylated product was dissolved in ether and injected into a DC 710 v.p.c. column (Model F & M 700, temperature 200 °C). Three peaks appeared with retention times at 0.95, 1.45, and 3.75 min. The retention time of an authentic sample of anisole-2,3,5,6-tetracarboxylic acid methyl ester (8) was 3.75 min.

Trimethyl Viopurpurin (3a)

Viopurpurin triacetate (**3***b*) (40 mg) was dissolved in absolute methanol. A methanol solution of sodium methoxide was added with stirring. The orange colored solution turned blue slowly. After stirring for 2 h, the solvent was removed and methyl iodide added to destroy the excess sodium methoxide. The resulting blue solid was suspended in 20 ml of spectrograde acetone, and 2 g of anhydrous potassium carbonate and 5 ml of dimethyl sulfate were added to the acetone solution. The mixture was refluxed for 8 h. After cooling, the solid was removed. The solvent was taken off by evaporating *in vacuo*. The excess dimethyl sulfate was hydrolyzed by stirring with 5% aqueous sodium hydroxide for 3 h. After the hydrolysis was complete, the alkaline solution was acidified with concentrated hydrochloric acid and extracted with chloroform; 30 mg of red crystalline trimethyl viopurpurin were obtained.[6] Recrystallization from methanol gave blood-red crystals, m.p. 173–174 °C.

λ_{max} (EtOH) 355 mμ (ε 1220), 278 mμ (ε 24 600), 270 mμ (ε 24 000), 218 mμ (ε 14 000); λ_{max} ($CHCl_3$) 455 mμ (ε 1030).

The mass spectrum showed a molecular ion peak at *m/e* 586 (calcd: 586). The n.m.r. of **3***a* showed the following peaks: δ 1.58 (6H, d), 3.10 (4H, d), 4.70 p.p.m. (2H, multiplet), corresponding to $CH_3CH(O)CH_2$—Ar; 7.8 (1H, s), 7.88 p.p.m. (1H, s) corresponding to two aromatic hydrogens; 4.11 (6H, s), 4.15 (3H, s), 4.2 p.p.m. (3H, s) corresponding to four methoxy groups.

[6]The material was used for degradation work. No analysis was obtained.

Alkaline Hydrogen Peroxide Oxidation of Trimethyl Viopurpurin (3a)

Trimethyl viopurpurin (20 mg) was dissolved in 5 ml of methanol and 5 ml of 20% sodium hydroxide was added. To the solution, 10 ml of 50% hydrogen peroxide was added slowly with stirring. Stirring was continued for 5 h, when the intense orange color faded to pale amber. The solution was then acidified with concentrated hydrochloric acid and extracted with ether in a liquid–liquid extractor for 24 h. The ether solution was evaporated to dryness: 3 mg of lactone **6** were obtained which on recrystallization from ether had a m.p. 192–194°. The m.p. was not depressed upon admixture of an authentic sample, and the i.r. spectrum and R_f value (t.l.c.) were identical with those of an authentic sample (5).

Acknowledgments

We would like to thank Dr. Ulrich Weiss, Laboratory of Physical Biology, National Institute of Arthritis and Metabolic Diseases, for taking the optical rotatory dispersion measurements, and Professor K. Mislow, Princeton University, for valuable suggestions.

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Some derivatives of 1-benzazepine

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A new rearrangement of a substituted 5*H*-1-benzazepine-5-one is described. A new route to certain dimethyl-1-benzazepines has been developed and linked up with a known synthesis. Several new derivatives of 1-benzazepine are reported.

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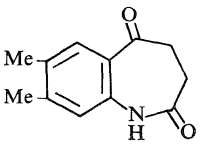
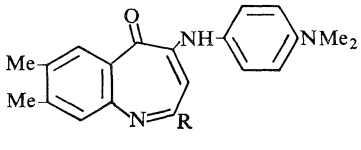
A number of 1-benzazepines based on the ketolactam **1**, (R = R′ = Me) have been described (1) and screened for pharmacological activity (2). Continuing our studies of this heterocyclic system, although we were unable to prepare analogues **1**, (RR′ = $(CH_2)_3$) and **1**, (R = Cl, R′ = Me) based on 5-acetylaminoindane and 3-methyl-4-chloroacetanilide respectively, we

were able to make various modifications to the heterocyclic ring.

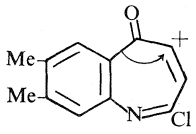


1



2

7,8-Dimethyl-2-hydroxy-4-(4′-dimethylamino)phenylamino-5*H*-1-benzazepine-5-one (**2**, R = OH) (1) was converted by phosphorus oxychloride into the corresponding 2-chloro-derivative (**2**, R = Cl). Reduction of the latter has so far given only a ring dihydro-derivative still containing the chlorine atom. During removal of the basic sidechain by acid hydrolysis (1), ring contraction occurred (3) to give the known 2-chloro-6,7-dimethylquinoline-4-carboxylic acid (4), presumably via the ion **3**. This is a new reaction of the sensitive "azatropone" system (5).



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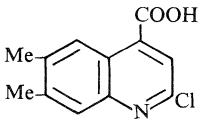
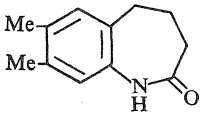


4

We have also developed a new route to 6,7-dimethyl-1-benzazepines based on β-3,4-xyloyl-propionic acid via reduction, cyclization to the tetralone, and Beckmann rearrangement of the ketoxime to give the lactam **5**.



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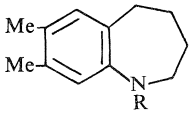
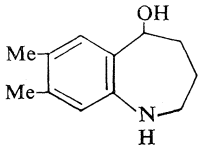


6

Subsequent hydride reduction gave the amine **6**, (R = H). Dehydration of the known alcohol **7** (1), followed by hydrogenation, gave a product shown to be the amine **6**, (R = H) by m.p., mixture m.p., and infrared (i.r.) spectrum, thus proving that both routes led to the same series of compounds.

The ketolactam **1**, (R = R′ = Me) was reduced by borohydride to the alcohol **8** providing a potential route to still further compounds.

Among variations of our original synthesis (1) of 1-benzazepines, we investigated the use of



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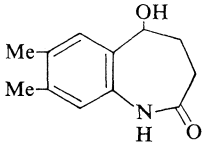
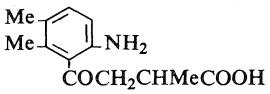


8

methylsuccinic anhydride and of *N*-methyl-*N*-acetyl-3,4-xylidine. To our surprise, the nuclear magnetic resonance (n.m.r.) spectra of compounds from these series showed the two aromatic protons as AB quartets, (J = 7 c.p.s.), suggesting structures **9** and **10** for the amino-acids isolated. The n.m.r. spectra of lactams **1**, (R = R′ = Me) and **5**, showed the aromatic protons as uncoupled (para-) singlets, confirming their orientation.

Although the amino-acids **9** and **10** might ultimately lead to 1-benzazepines, these were not prepared as they would be 6,7-dimethyl-1-benzazepines, whereas our thesis is (2) that maximum pharmacological activity would lie in the 7,8-dimethyl series.

Further work in this field continues.



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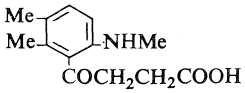

10

Experimental

7,8-Dimethyl-2-chloro-4-(4′-dimethylamino)phenylamino-5H-1-benzazepine-5-one (2, R = Cl)

The red 2-hydroxy compound **2**, (R = OH), (9.8 g) (1) was heated for 1 h on a steam bath with phosphorus oxychloride (25 ml). The solution was cooled and poured onto ice to decompose excess acid chloride, then filtered to remove a brown substance (0.3 g). On neutralization, the deep-red 2-chloro derivative was precipitated. It was collected and washed with 0.5 *N* carbonate solution, then water, and dried, to give a yield of 8.3 g, m.p. 230° from toluene.

Anal. Calcd. for $C_{20}H_{20}ClN_3O$: C, 67.9; H, 5.7; Cl, 10.0; N, 11.9. Found: C, 68.2; H, 5.8; Cl, 10.2; N, 11.6.

The carbonate washings, on acidification, gave 0.4 g of 7,8-dimethyl-3-hydro-1*H*-1-benzazepine-2,4,5(3*H*)-trione (1).

Catalytic hydrogenation or chromous chloride reduction of compound **2**, (R = Cl), gave the same yellow compound, m.p. 180–200° from aqueous acetic acid. This compound was difficult to purify but analyzed roughly for the acetate monohydrate of the dihydro derivative.

Acid Hydrolysis of the Chloro Compound (2, R = Cl)

The above chloro compound had λ_{max} 395, 280, and 225 mμ, log ε 4.06, 4.34, and 4.71 respectively, in ethanol

but gave an unstable spectrum in acid. On a preparative scale, the chloro compound was boiled with dilute hydrochloric acid until the color had faded. The filtered solution was neutralized, giving a carboxylic acid m.p. 217° from acetic acid, spectroscopically identical with and undepressed in mixed melt by 2-chloro-6,7-dimethylquinoline-4-carboxylic acid, prepared according to the literature (4).

7,8-Dimethyl-3,4,5-trihydro-1H-1-benzazepine-2(H)-one (5)

6,7-Dimethyl-1-tetralone (6) was treated with hydroxylamine hydrochloride in ethanolic pyridine at reflux. Addition of water gave the oxime, m.p. 179°.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 8.0; N, 7.4. Found: C, 75.75; H, 7.85; N, 7.35.

Beckmann rearrangement (7) of the oxime gave the azepinone (**5**), m.p. 175° from ligroin.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 8.0; N, 7.4. Found: C, 76.55; H, 8.3; N, 7.4.

7,8-Dimethyl-2,3,4,5-tetrahydro-1H-1-benzazepine (6, R = H)

The azepinone (**5**) gave on hydride reduction (8), the amine **6**, (R = H), m.p. 82° after sublimation.

Anal. Calcd. for $C_{12}H_{17}N$: C, 82.2; H, 9.8; N, 8.0. Found: C, 82.0; H, 9.8; N, 8.0.

The amine was characterized as its picrolonate, m.p. 205°, crystallized from dioxan.

Anal. Calcd. for $C_{22}H_{25}N_5O_5$: C, 60.1; H, 5.7; N, 15.95. Found: C, 60.0; H, 5.7; N, 15.9.

The *N*-acetyl derivative **6**, (R = CH_3CO) had m.p. 90° when crystallized from aqueous ethanol.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.4; H, 8.8; N, 6.45. Found: C, 77.05; H, 8.9; N, 6.5.

Dehydration and Subsequent Hydrogenation of 5-Hydroxy-7,8-dimethyl-2,3,4,5-tetrahydro-1H-1-benzazepine (7)

The above azepine (**7**) (1 g) (1) was refluxed with concentrated hydrochloric acid (6 ml). On cooling, crystals of the hydrochloride of the dehydrated base appeared, m.p. 196°.

Anal. Calcd. for $C_{12}H_{16}ClN$: C, 68.7; H, 7.7; N, 6.7; Cl^-, 16.9. Found: C, 68.65; H, 7.5; N, 6.6; Cl^-, 17.0.

This salt was alkalized and a benzene extract washed until neutral, then evaporated, giving the free base, 7,8-dimethyl-2,3-dihydro-1*H*-1-benzazepine (1). This in turn was hydrogenated in ethanol using Adam's catalyst, giving the tetrahydrobenzazepine **6**, (R = H), m.p. 82°, which was undepressed in mixed melt, and the infrared (i.r.) spectrum was superimposable with that of the sample made by the other route.

5-Hydroxy-7,8-dimethyl-3,4,5-trihydroxy-1H-1-benzazepine-2(H)-one (8)

The ketolactam **1**, (R = R′ = Me) in tetrahydrofuran was treated with excess sodium borohydride in water. The mixture was neutralized with dilute acetic acid and extracted with hot benzene giving on cooling, the hydroxy compound (**8**), m.p. 192°. The i.r. spectrum confirmed the structure.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.2; H, 7.4; N, 6.8. Found: C, 70.5; H, 7.35; N, 6.6.

Friedel–Crafts Reaction of N-Acetyl-3,4-xylidine with Methylsuccinic Anhydride

The above amide (81.7 g) gave (1) the keto-acid (55.4 g) assumed to be the α-methyl isomer (9), m.p. 206°, crystallized from ethanol.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.95; H, 6.9; N, 5.05. Found: C, 64.85; H, 7.0; N, 5.05.

Hydrolysis with 6 *N* hydrochloric acid yielded the amino-acid hydrochloride, m.p. 143°, crystallized from 2 *N* acid.

Anal. Calcd. for $C_{13}H_{17}NO_3 \cdot HCl \cdot H_2O$: Cl^-, 12.4. Found: Cl^-, 12.1.

Recrystallization from aqueous ethanol resulted in hydrolysis of the salt, giving the free amino-acid, m.p. 173°, crystallized from toluene.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.4; H, 7.3; N, 6.0. Found: C, 66.4; H, 7.3; N, 6.5.

The nuclear magnetic resonance (n.m.r.) spectrum of the *N*-acetyl derivative showed *ortho* protons indicating structure **9**.

N-Acetyl-N-methyl-3,4-xylidine

N-Formyl-3,4-xylidine (10), b.p. 134°/0.4 mm was reduced by lithium aluminium hydride (8) to *N*-methyl-3,4-xylidine, b.p. 170°/110 mm, n_D^{22} 1.553, lit.(11) 1.558; picrate m.p. 139°, lit. 133–136°. The picrolonate had m.p. 205° decomp., crystallized from ethanol.

Anal. Calcd. for $C_9H_{21}N_5O_5$: N, 17.5. Found: N, 17.6.

The above methylxylidine (20 g), after refluxing for 2 h with acetic anhydride (20 ml) then distilling, gave the *N*-acetyl derivative (23.7 g) b.p. 202°/83 mm which had m.p. 76°, crystallized from cyclohexane.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.55; H, 8.55; N, 7.9. Found: C, 74.65; H, 8.65; N, 7.95.

The above methyl-xylidine, after reflux for 1 h with succinic anhydride (1 equivalent) in dioxan, gave on precipitation with water, the *N*-succinoyl derivative, m.p. 102°, crystallized from benzene/cyclohexane.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.4; H, 7.3; N, 5.95. Found: C, 66.6; H, 7.6; N, 5.8.

Friedel–Crafts Reaction of N-Methyl-N-acetyl-3,4-xylidine with Succinic Anhydride

The above amide (24.3 g) gave (1) the crude keto-acid in benzene solution. After extraction with dilute alkali, starting amide (10 g) remained in the benzene. The alkaline extract was acidified, precipitating the keto-acid as an oil which was triturated with ether leaving insoluble material (2 g). The ether solution was washed with water, dried, and the solvent evaporated leaving a golden brown oil (10.8 g) which did not crystallize. It was therefore hydrolyzed with 6 *N* hydrochloric acid (40 ml) at the reflux (3 h), then concentrated to 20 ml. Neutralization gave an oil which was stored in vacuum until partly solid. After pressing this on a porous plate, a tacky solid remained which was triturated with methanol to give pure amino-acid (1.85 g), m.p. 118°, crystallized from aqueous ethanol.

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.35; H, 7.3; N, 5.95. Found: C, 66.0; H, 7.3; N, 5.85.

The n.m.r. spectrum of the amino-acid revealed *ortho* protons, indicating structure **10**.

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Metallation of 5- and 6-membered ring sultones

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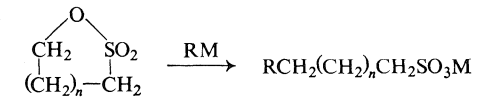
Treatment of 1,3-propane and 1,4-butane sultone with *n*-butyllithium in tetrahydrofuran at −78° has been shown to result in metallation α to the sulfonyl group. This is in contrast to ring opening which has been observed when the reaction was carried out at room temperature (1, 2). The products obtained from the interaction of the lithio derivatives **3** and **4** with carbonyl compounds and alkyl halides are described.

Canadian Journal of Chemistry, 47, 1230 (1969)

The reaction of 5- and 6-membered ring sultones with a wide variety of nucleophilic reagents such as alcohols, amines, alkoxides, and metal alkyls has been reported to lead invariably to derivatives of sulfonic acids, see eq. [1] (1, 2). This type of reaction has been of considerable industrial importance since it has allowed the introduction of a water-solubilizing group into a variety of organic molecules.

[1] 

1, $n = 1$
2, $n = 2$

The reactions of **1** and **2** with the organometallic reagents were generally carried out at temperatures above 0° (2). We have found that if the treatment of the sultones with alkyllithiums, e.g. *n*-butyllithium, is carried out at acetone – dry ice temperature in tetrahydrofuran solution, the ring opening reaction is suppressed and metallation occurs α to the sulfonyl group, thereby yielding the lithio salts **3** and **4** as shown by quantitative deuterium incorporation upon hydrolysis with D_2O. The success of the metallation procedure at the low temperature apparently stems from the fact that the ring opening reaction is considerably more temperature dependent than metallation. Metallation α to the sulfonyl groups of aliphatic sulfonic acid esters has recently been reported by Corey and Durst (3).

The lithio derivatives appeared to be stable for at least 3 h in tetrahydrofuran solution at −78°. Decomposition occurred rapidly upon warming to −20° as evidenced by the formation of a colorless water-soluble precipitate. The infrared (i.r.) spectrum (KBr) of this material showed only a few ill-defined bands; its structure has not been further investigated.

Reaction of **3** and **4** with carbonyl derivatives afforded, after hydrolysis, the adducts **5** and **6** in 65–85% yield. The structures of the adducts were assigned on the basis of elemental analyses and spectroscopic properties. The i.r. spectrum of each adduct showed a moderately strong band at about 3550 cm^{-1} due to the newly formed hydroxyl group and strong bands between 1340–1360, 1160–1170, and 980–995 cm^{-1} which indicated that the sultone grouping had been retained. Nuclear magnetic resonance (n.m.r.) data (see Experimental) fully supported the above conclusions.