whose infrared spectrum was identical with that of the base obtained on treating the hydrochloride of **1d** with base.

The reaction of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol-d_5 (1c-d_5) hydrochloride with *p*-toluenesulfonyl chloride by the method above gave 1-methyl-3-chloro-4-phenyl-1,2,3,6-tetrahydropyridine-*d* (**1d**-*d*) hydrotosylate. Recrystallization of this solid from wet isopropyl alcohol gave white plates, mp 202–203°. Integration of the nmr spectrum of the free base indicated that the deuterium label was divided evenly between the 3 and 5 positions.

1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridyl Acetate (1e) Hydrobromide.—A solution of 8.5 g (0.045 mole) of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (**1c**) and 1.5 g of sodium acetate in 60 ml of acetic anhydride was heated under reflux for 6 hr and cooled in an ice bath. The mixture was made basic with an excess of potassium carbonate and the water layer was extracted three times with 50-ml portions of ether. The combined organic layers were dried over potassium carbonate and evaporated to give a dark oil. Dissolution of this oil in acetone followed by treatment with hydrogen bromide gave, in three crops, 11.5 g (81%) of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridyl acetate (**1e**) hydrobromide. Recrystallization from ethanol gave an analytical sample, mp 230–232°, $\lambda_{max}^{H_2O}$ 240 mμ (log ε 4.07).

Anal. Calcd for $C_{14}H_{18}BrNO_2$: C, 53.86; H, 5.81; N, 4.49. Found: C, 53.88; H, 5.87; N, 4.74.

The Solvolysis of 1-Methyl-3-chloro-4-phenyl-1,2,3,6-tetrahydropyridine (1d) Hydrobromide.—A solution of 0.8 g (0.02 mole) of sodium hydroxide in 10 ml of water was added to 1.0 g (4 moles) of **1d** hydrochloride in 10 ml of water. The mixture was heated at 80° for 1 hr, cooled, and extracted four times with 50-ml portions of ether. The combined organic layers were dried over potassium carbonate and evaporated to give 0.75 g (100%) of a yellow solid. Gas chromatographic analysis of this solid on a 1-m Carbowax 20M column indicated that it contained only one volatile component. Recrystallization of this solid from *n*-heptane gave 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (**1c**), mp 101–103°.

The Solvolysis of 1-Methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine (1b) Hydrobromide. A.—A solution of 0.5 g (0.5 mmole) of **1b** in 15 ml of water was heated on a steam bath for 0.5 hr. Isolation as above gave 0.23 g (83%) of **1c**, mp 101–103°, as shown by infrared spectrum and vpc retention time.

B.—A solution of 0.3 g (8 mmoles) of sodium hydroxide in 5 ml of water was added to a solution of 1.0 g (3 mmoles) of **1b** in 50 ml of water and stirring was maintained at room temperature for 2 hr. Isolation as above gave 0.40 g (70%) of a pale yellow solid. Recrystallization of the solid from *n*-heptane gave 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (**1c**), mp 99–102°, as shown by vpc retention time and infrared spectrum.

The Reaction of 1-Methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine (1b) Hydrobromide with Weak Aqueous Base.—To a mixture of an aqueous solution of potassium carbonate and ether was added 1.0 g (3 mmoles) of 1-methyl-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridine (**1b**) hydrobromide. The mixture was shaken until, on standing, both layers were homogeneous. The water layer was drawn off and the ether layer was dried over potassium carbonate. The organic layer was evaporated and the solid residue was triturated with acetone. Recrystallization from water gave 0.2 g (18%) of a white solid, mp 238–241°. The infrared spectrum of the solid had a broad band at 3400 cm^{-1}; the elemental analyses were correct for a dimer plus a molecule of water, and the ultraviolet spectrum indicated the presence of two isolated styryl groups. A likely structure for this compound is 1-methyl-1-[3-(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridyl)]-3-bromo-4-phenyl-1,2,3,6-tetrahydropyridinium bromide monohydrate; $\lambda_{max}^{H_2O}$ 245 mμ (log ε 4.34).

Anal. Calcd for $C_{24}H_{30}Br_2N_2O$: C, 55.19; H, 5.79; N, 5.36; Br, 30,60. Found: C, 54.92; H, 5.96; N, 4.73. Found (Mohr method): Br, 30.85.

The Attempted Thermal Rearrangement of 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridyl Acetate (1e).—A sample of the acetate **1e**, mp 78–80°, was distilled under aspirator pressure. The distillate was collected as a single fraction with the largest amount boiling from 177–179°. The product was identified by its vpc retention time and infrared spectrum as unrearranged **1e**. The analysis by gas chromatography showed that within the limits of detection no rearrangement had occurred.

The Hydrolysis of 1-Methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridyl Acetate (1e).—A mixture of 1.1 g (5 mmoles) of **1e** and water was heated above the melting point of the organic material, and a solution of 0.8 g of sodium hydroxide in 5 ml of water was added. The mixture was heated under reflux for 24 hr and cooled to 10° in an ice bath. The solid which separated was collected by filtration, dissolved in ether, and dried over potassium carbonate. The vapor phase chromatographic analysis of this solution indicated the presence of only one volatile component which was identified by its retention time as 1-methyl-4-phenyl-1,2,3,6-tetrahydro-3-pyridinol (**1c**). Evaporation of the ether gave a white solid, mp 101–104°, after recrystallization from *n*-heptane. This solid was shown by infrared spectrum to be **1c**.

Registry No.—**1b**, 14164-47-7; **1b**-HBr, 14164-48-8; **1b**-*d*, 14164-49-9; **1c**, 1891-24-3; **1c**-HCl, 13427-23-1; **1c**-d_5, 14271-26-2; **1d**, 14164-52-4; **1d**-HCl, 14271-27-3; **1d**-hydrotosylate, 14164-53-5; (**1d**-*d*)-HCl, 14164-54-6; **1d**-*d*-hydrotosylate, 14164-55-7; **1e**, 14164-56-8; **1e**-HBr, 14164-57-9; **3**, 14164-58-0.

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The Reduction of Some Flavylium Salts With Sodium Borohydride

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Reduction of flavylium perchlorate with sodium borohydride in several primary alcohols gave dimers which were assigned structures **3a**, **3b**, and **3c**. A mechanism for this reaction is postulated. The reduction was carried out in acetonitrile and *t*-butyl alcohol and the product was found to be 4H-flavene (**2**). Several substituted flavylium salts were reduced by means of sodium borohydride in ethanol and structures were assigned to the products.

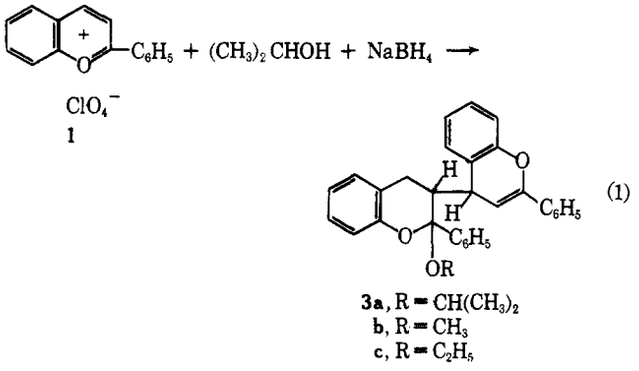
Only few examples of the reduction of pyrylium or flavylium salts by means of metal hydride reducing agents have appeared in the literature. Recently, it was shown[1] that the reduction of 2,4,6-trimethylpyrylium perchlorate by means of sodium borohydride in ether gives two dienones which no longer possess a cyclic structure.

Since flavylium salts are more resistant to ring cleavage than are pyrylium salts, we thought that it would be of interest to investigate the reduction of flavylium

(1) A. T. Balaban, G. Mihai, and C. D. Nenitzescu, *Tetrahedron*, **18**, 257 (1962).

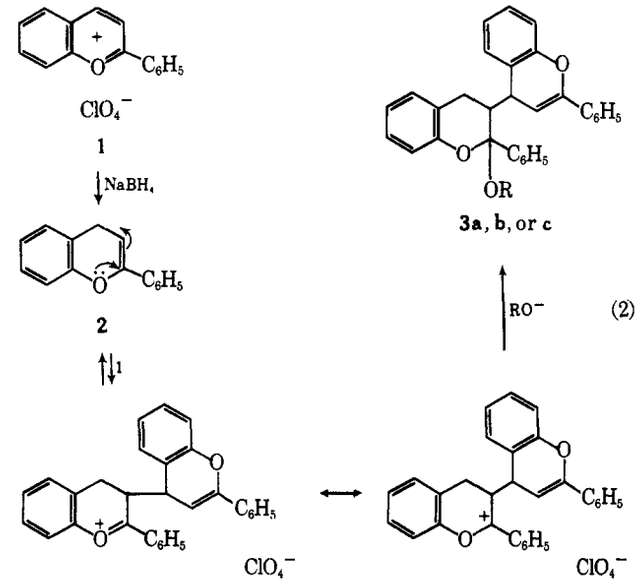
perchlorate (**1**) with sodium borohydride. It had been reported[2] that flavylium chloride reduced in ether by lithium aluminum hydride gives 4H-flavene (**2**), but no examples of the reduction of a flavylium salt with sodium borohydride were found in the literature.

We found that the reaction of flavylium perchlorate (**1**) in isopropyl alcohol with sodium borohydride (eq 1) gives an unexpectedly complicated product which was assigned structure **3a** on the basis of elemental analysis, mass spectrum, and nmr spectrum. When



(1)

the reaction was carried out in methanol or ethanol rather than in isopropyl alcohol, the products **3b** and **3c** were obtained. The solvents, acetonitrile and *t*-butyl alcohol, led to the formation of 4H-flavene (**2**).[3] A reasonable mechanism for the formation of the dimers **3a**, **3b**, and **3c** is shown in eq 2.



(2)

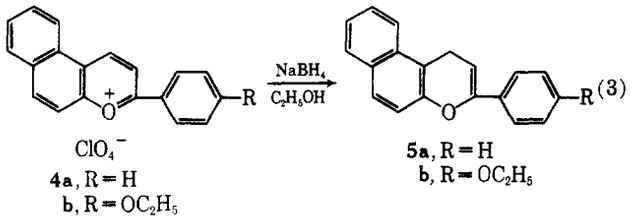
Additional evidence for this course of reaction was obtained when it was shown that a mixture of **1**, **2**, and sodium acetate in isopropyl alcohol, methanol, or ethanol gave **3a**, **3b**, or **3c**. The fact that **1** and sodium borohydride in acetonitrile or *t*-butyl alcohol gave only the 4H-flavene is evidence that the formation of a dimer was dependent on the presence of a nucleophile in the reaction medium. An additional factor that led to dimer formation was the insolubility of **1** in alcohols, thus ensuring that there was some unreacted **1** present to undergo reaction with the reduction product **2**.

(2) K. G. Marathe, E. M. Philibin, and T. S. Wheeler, *Chem. Ind.* (London), 1793 (1962).

(3) For a good laboratory method for the preparation of 4H-flavene, see J. A. VanAllan, G. A. Reynolds, and T. H. Regan, *J. Org. Chem.*, **32**, 1897 (1967).

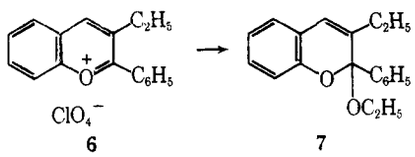
The mechanism just postulated for the formation of dimers is similar to the mechanism which has been proposed[4] for the formation of tetrahydropyridines from quaternary salts and sodium borohydride.

The reduction by means of sodium borohydride in ethanol was extended to the pyrylium salts **4a** and **4b** and the products isolated were the 1,4-pyranes **5a** and **5b** (eq 3). The failure of **4a** and **4b** to condense with **5a** and **5b** to give dimers was probably due to steric factors.



(3)

The attempted reduction of 3-ethylflavylium perchlorate (**6**) with sodium borohydride in ethanol unexpectedly yielded **7** (eq 4). It is evident that the reducing agent acted only as a base in this case, and, in fact, treatment of **6** with sodium hydroxide and ethanol also gave **7**.



(4)

Experimental Section

3-Flaven-4-yl-2-isopropoxyflavane (3a).—A suspension of 5 g of flavylium perchlorate (**1**) in 100 ml of isopropyl alcohol was stirred and 1 g of sodium borohydride was added in several portions. The reaction mixture was completely decolorized in a short time. After the mixture had been stirred for 0.5 hr, the white solid that separated was collected and recrystallized from isopropyl alcohol to yield 2.2 g of product (**3a**), mp 136–137°.

Anal. Calcd for $C_{33}H_{30}O_3$: C, 83.4; H, 6.4. Found: C, 83.3; H, 6.4.

The mass spectrum of **3a** showed a parent peak at 475 mass units and fragmentation typical of isopropyl alcohol and 4H-flavene. The nmr spectrum[5] of **3a** (in $CDCl_3$) had the following absorption: $(CH_3)_2$–C–O, τ 9.09 (d) and 9.19 (d), six protons; aliphatic ring protons, 6.48–7.5 (m), four protons; Me_2CH–O, 6.0 (q), one proton; vinyl proton, 4.68 (d); aromatic protons, 18 protons.

3-Flaven-4-yl-2-methoxyflavane (3b).—This compound was prepared by the method just described for **3a** with methanol as the solvent. The product was recrystallized from methanol to give 2 g of **3b**, mp 204°.

Anal. Calcd for $C_{31}H_{26}O_3$: C, 83.1; H, 5.9. Found: C, 82.8; H, 5.8.

The mass spectrum showed a parent peak at 447 mass units and fragmentation typical of methanol and 4H-flavene. The nmr spectrum was nearly identical with that of **3a**, except that absorption of the methoxy protons replaced those of the isopropoxy group.

2-Ethoxy-3-flaven-4-ylflavane (3c).—The product, which was also prepared by the method described for **3a** with ethanol as the solvent, was obtained in a 2.5-g yield (from ethanol) and melted at 169–170°.

Anal. Calcd for $C_{32}H_{28}O_3$: C, 83.4; H, 6.1. Found: C, 83.2; H, 6.2.

(4) R. E. Lyle, D. A. Nelson, and P. S. Anderson, *Tetrahedron Letters*, 553 (1962); P. S. Anderson and R. E. Lyle, *ibid.*, 153 (1964).

(5) The nmr spectra were measured at 60 Mc on a Varian A-60 spectrometer with tetramethylsilane as an internal standard.

The mass spectrum showed a parent peak at 461 mass units and fragmentation typical of ethanol and 4H-flavene. The nmr spectrum was like that of **6** except for absorption by the ethoxy protons.

The preparation of **3a**, **3b**, and **3c** by the reaction of flavylium perchlorate (**1**) and 4H-flavene (**2**) is illustrated by the preparation of **3c**. A solution of 3 g of **1**, 2 g of **2**, 1.5 g of sodium acetate, and 75 ml of ethanol was stirred for 2 hr. Some white solid began to precipitate in a short time. The reaction mixture was diluted with 15 ml of water, and the solid was collected and recrystallized from ethanol to give 2.4 g of **3c**, mp 169–170°.

4H-Flavene (2).—To a stirred solution of 5 g of flavylium perchlorate in 100 ml of acetonitrile was added 1 g of sodium borohydride in portions. The colorless solution was diluted with some water to destroy the excess sodium borohydride and then evaporated to dryness on a rotary evaporator. The residue was extracted with ether, the extract was dried (magnesium sulfate), and the ether was removed. The residue was recrystallized from methanol to yield 2.6 g of product, mp 54–55°. The melting point and infrared spectrum of the product were identical with those of a sample prepared previously.[3]

Anal. Calcd for $C_{15}H_{12}O$: C, 86.6; H, 5.8. Found: C, 86.5; H, 5.7.

The nmr spectrum (in deuteriochloroform) showed a doublet centered at τ 6.45 (two protons), a triplet centered at 4.32 (one proton), and a multiplet centered at 2.4 (nine protons).

Essentially, the same results were obtained when flavylium perchlorate was treated with sodium borohydride in *t*-butyl alcohol, although the yield of **2** was slightly less.

2-Phenylnaphtho[2,1-*b*]-4H-pyran (5a).—A mixture of 3 g of 2-phenylnaphtho[1,2-*b*]pyrylium perchlorate (**4a**), 100 ml of ethanol, and 0.5 g of sodium borohydride was stirred for 1 hr and diluted with 200 ml of water, and the solid was collected and recrystallized from toluene to give 1.5 g of **5a**, mp 186–187°.

Anal. Calcd for $C_{19}H_{14}O$: C, 88.4; H, 5.4. Found: C, 88.5; H, 5.3.

The nmr spectrum (in deuteriochloroform) showed two methylene protons (doublet) at τ 6.22; one vinyl proton (triplet) at 4.4; and 11 aromatic protons over the range 2.1–2.9.

2-(4-Ethoxyphenyl)naphtho[2,1-*b*]-4H-pyran (5b).—This compound was prepared by the procedure described for the preparation of **5a** and the product (1.4 g) melted at 174°.

Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.4; H, 6.0. Found: C, 83.6; H, 6.3.

2-Ethoxy-3-ethyl-2H-flavene (7).—To a suspension of 3 g of 3-ethylflavylium perchlorate (**6**) in 70 ml of ethanol was added 0.7 g of sodium borohydride. The solid quickly dissolved to give a pale yellow solution. The solution was stirred for 15 min and then diluted with 100 ml of water. The oil that separated was extracted with methylene chloride, the extract was dried (magnesium sulfate), and the solvent was removed. The residue was distilled to give 1.8 g of **15**, bp 134° (0.3 mm).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.4; H, 7.1. Found: C, 81.5; H, 7.1.

The nmr spectra (in deuteriochloroform) had the following absorption: CH_3–, τ 8.79 (t), J = 7 cps, and 9.08 (t), J = 7 cps; $MeCH_2$–, τ 8.04 (split q); $MeCH_2O$–, τ 6.45 (q), J = 7 cps; vinyl H, τ 3.5 (s); nine aromatic protons.

A solution of 2 g of 3-ethylflavylium perchlorate (**6**), 20 ml of ethanol, and 5 ml of 40% sodium hydroxide solution was allowed to stand overnight and diluted with 100 ml of water; the oil that separated was extracted with ether. The extract was dried (magnesium sulfate), the solvent was removed, and the residue was distilled to give 2.1 g of product which had an infrared absorption spectrum which was identical with that of the sample of **7** prepared by the sodium borohydride procedure.

Registry No.—2, 494-13-3; **3a**, 14319-49-4; **3b**, 14161-90-1; **3c**, 14161-91-2; **5a**, 14271-36-4; **5b**, 14161-92-3; **7**, 14161-93-4; sodium borohydride, 1303-74-8.

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1,2,5,6-Tetrahydro-12H-pyrrolo[1′,2′:1,2]azepino[3,4-*b*]indoles and 5H,7H,14H-8,9-Dihydroisoindolo[2′,1′:1,2]azepino[3,4-*b*]indoles[1]

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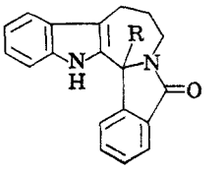
The reaction products from 3-(3-aminopropyl)indole and γ-keto acids and phthalaldehydic acid varied with the structure of the acid used. *o*-Benzoylbenzoic acid gave 5-oxo-5H,7H,14H-8,9-dihydro-14b-phenylisoindolo[2′,1′:1,2]azepino[3,4-b]indole (Ia). *o*-Acetylbenzoic acid gave 2-[3-(3-indolyl)propyl]-3-methylenephthalimidine (II) which was cyclized to the tetrahydroazepine (Ib) with acid. Phthalaldehydic acid gave amorphous products. The tetrahydroazepine (Ic) was synthesized from the phthalimide derivative of 3-(3-aminopropyl)indole. The γ-lactones of 4-hydroxy-4-phenyl-3-butenoic acid and 4-hydroxy-3-pentenoic acid were used to synthesize the 1,2,5,6-tetrahydro-12H-pyrrolo[1′,2′:1,2]azepino[3,4-*b*]indole derivatives (VIII). Lithium aluminium hydride reduction of the various lactams gave the corresponding amines in all cases except Ic.

The successful synthesis of pyrrolo-β-carbolines[2] and the indolo-β-carbolines[3] from tryptamine and γ-keto acids and phthalaldehydic acids suggested a study of the condensation of 3-(3-aminopropyl)indole with phthalaldehydic acid and γ-keto acids as a method for the preparation of substituted azepines. The reaction products obtained differed with the structure of the acid used.

o-Benzoylbenzoic acid was the only acid which gave lactam Ia directly under the condition used previously.[2] Proof for the structure of Ia was a negative Ehrlich test and the infrared spectrum.

The condensation of *o*-acetylbenzoic acid with 3-(3-aminopropyl)indole did not give the expected lactam



Ia, R = C_6H_5
b, R = CH_3
c, R = H

(1) Abstracted in part from the Ph.D. Thesis of M. M. Maynard, State University of Iowa, June 1966.

(2) S. Wawzonek and J. D. Nordstrom, *J. Med. Chem.*, **8**, 265 (1965).

(3) S. Wawzonek and G. E. Nelson, *J. Org. Chem.*, **27**, 1377 (1962).