Flavonoids. VI. Synthesis and Structure of Isomeric N-Pyrrolidinomethylisoflav-3-enes[1]

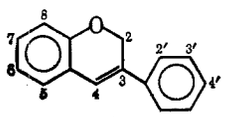
C. E. COOK AND MONROE E. WALL

Chemistry and Life Sciences Laboratory, Research Triangle Institute, Research Triangle Park, North Carolina

Received February 9, 1968

The Mannich reaction[2] provides a convenient method for the introduction of substituents into phenolic compounds, since the reactivity of the resulting dialkylaminomethyl group is such that it may be converted into a variety of other groups. We report here the application of the Mannich reaction to the synthesis of pyrrolidinomethylisoflav-3-enes, the orientation of which (readily established by nmr spectra) was found to depend upon the route of preparation.

Treatment of the hydroxycoumarin **1**[3] with formaldehyde and pyrrolidine[4] gave a 90% yield of a pyrrolidinomethylcoumarin (**2**) which reacted with methyl Grignard reagent to give crude triol **3** (Scheme I). The potential heterocyclic ring was not closed at this point, since there was no ultraviolet maximum above 300 mμ. However, when crude **3** was heated in excess hydrochloric acid, the solution exhibited a new maximum at 310 mμ,[3] and a salt precipitated. Decomposition of the salt with bicarbonate gave the isoflavene **4a**.



i

When the isoflavene **5**[3] was subjected to the Mannich reaction, the product was an isomeric pyrrolidinomethylisoflav-3-ene (**6a**). Nmr spectra[5] of the aromatic hydrogens clearly distinguished isomers **4a** and **6a**. The C-5 and C-6 protons of **4a** appeared as a pair of doublets at δ 7.04 and 6.43, with J = 8.6 cps as expected for *ortho* protons, whereas in **6a** the C-5 and C-8 protons gave sharp singlets (*para* hydrogens) at δ 6.82 and 6.36.

In both cases the signals at δ 7.04 and 6.82 were partially obscured by signals due to the 2′ and 3′ protons, but the acetoxymethyl acetates **4b** and **6b** (prepared by treating **4a** and **6a** with sodium acetate in acetic anhydride[4a]) showed quite clear-cut patterns. The C-5 and C-6 protons of **4b** were evidenced by a pair of doublets at δ 7.25 and 6.72 (J = 8 cps), whereas the *para* (5,8) hydrogens of **6b** gave singlets at δ 7.30 and 6.67. In all four compounds the pattern centered around 421 cps due to the other aromatic protons was practically identical, which is good evidence for its assignment. The peak farthest downfield in each case is assigned to the C-5 proton which lies in the deshielding region of the adjacent double bond.[6]

The 8 substitution of the 7-hydroxycoumarin **1** is consistent with the results of others,[4] and the isoflav-3-ene **4** reacts according to the pattern shown by resorcinol in, *e.g.*, acylation[7] or carboxylation[8] reactions.

Prolonged heating of isoflav-3-ene **5** with formaldehyde and pyrrolidine gave the bis adduct **7**, identified as such by integration of the nmr spectrum and analysis. The 8 position for the second pyrrolidinomethyl substituent is assigned on the basis of the *ortho–para* directing influence of the oxygen functions and on the nmr spectrum (singlet at δ 7.03; the signal at δ 6.36 present in **6a** is missing).

Experimental Section[5,9]

3-(*p*-Methoxyphenyl)-4-ethyl-7-hydroxy-8-(N-pyrrolidino)-methylcoumarin (2).—A solution of 20.0 g (67.6 mmol) of 3-(*p*-methoxyphenyl)-4-ethyl-7-hydroxycoumarin (**1**),[3] 11.2 ml of pyrrolidine, and 10.0 ml of 40% formalin in 500 ml of absolute ethanol was refluxed.[4] Tlc (1% acetic acid in 2-propanol on silica gel) indicated complete reaction at the end of 2 hr. The resulting mixture was chilled overnight and filtered to yield 24.3 g (94%) of **2**, mp 190–192° when placed in a bath preheated to 185°.

The compound could also be prepared by reaction in dimethoxyethane. Complete reaction occurred in 0.5 hr, but the yield was somewhat lower. Recrystallization could be carried out from acetonitrile, acetone, or preferably ethanol (*ca.* 40 ml/g), but with no change in melting point.

Anal. Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 73.19; H, 6.60; N, 3.92.

2,2-Dimethyl-4′-methoxy-4-ethyl-7-hydroxy-8-(N-pyrrolidino)-methylisoflav-3-ene (4a).—A solution of 15.0 g (39.5 mmol) of the coumarin **2** in 400 ml of dry tetrahydrofuran was treated with 100 ml of 3 *M* methylmagnesium bromide in ether. The solution was refluxed for 2 hr, cooled, and treated with a slurry of 100 g of NH_4Cl in 200 ml of water. The mixture was stirred for 15 min and filtered. Separation of layers and evaporation of the ether layer left an off-white solid (λ_{max} 285 mμ), which was heated with 220 ml of water and treated slowly with 1 *N* HCl until solution was complete. More HCl was added (total of 220 ml) and the yellow solution was heated on a steam bath for 1.25 hr. Overnight refrigeration yielded 15.2 g of an off-white solid which was shaken with 100 ml of sodium bicarbonate solution and 700 ml of ether until solution was complete. The ether layer was washed with water, dried, and evaporated to give a solid which was recrystallized twice from 2-propanol (9 ml/g) and once from absolute ethanol (14 ml/g) to yield a total of 11.4 g (73%), mp 150–151.5° with softening at 149°. Two more recrystallizations from ethanol gave the analytical sample (same melting point).

Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.38; H, 8.16; N, 3.65.

The infrared spectrum (CS_2) showed bands at 835 and 810 cm^{-1}. At high concentration bands were observed at 1882, 1760 (*para* disubstitution), 1852, and 1730 cm^{-1} (1,2,3,4-tetrasub-

(1) (a) Flavonoids. V: K. H. Dudley, H. W. Miller, R. C. Corley, and M. E. Wall, *J. Med. Chem.*, **10**, 985 (1967). (b) A portion of this work was presented at the 4th Annual Meeting of the Plant Phenolics Group of North America, July 1964. (c) This research was carried out under Contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health. (d) In accordance with common usage, compounds in this paper are named as derivatives of the isoflavan[3-aryl-1(2H)-benzopyran] nucleus, with the numbering shown in i.

(2) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942).

(3) C. E. Cook, R. C. Corley, and M. E. Wall, *J. Org. Chem.*, **30**, 4114 (1965).

(4) (a) P. Da Re, G. Bonola, and L. Verlicchi, *J. Med. Chem.*, **7**, 162 (1964); (b) R. B. Desai, *J. Org. Chem.*, **26**, 5251 (1961).

(5) Nmr spectra were determined at 60 Mhz in deuteriochloroform solution by S. Justice of this laboratory. Values are reported in δ (parts per million) or cycles per second relative to internal tetramethylsilane.

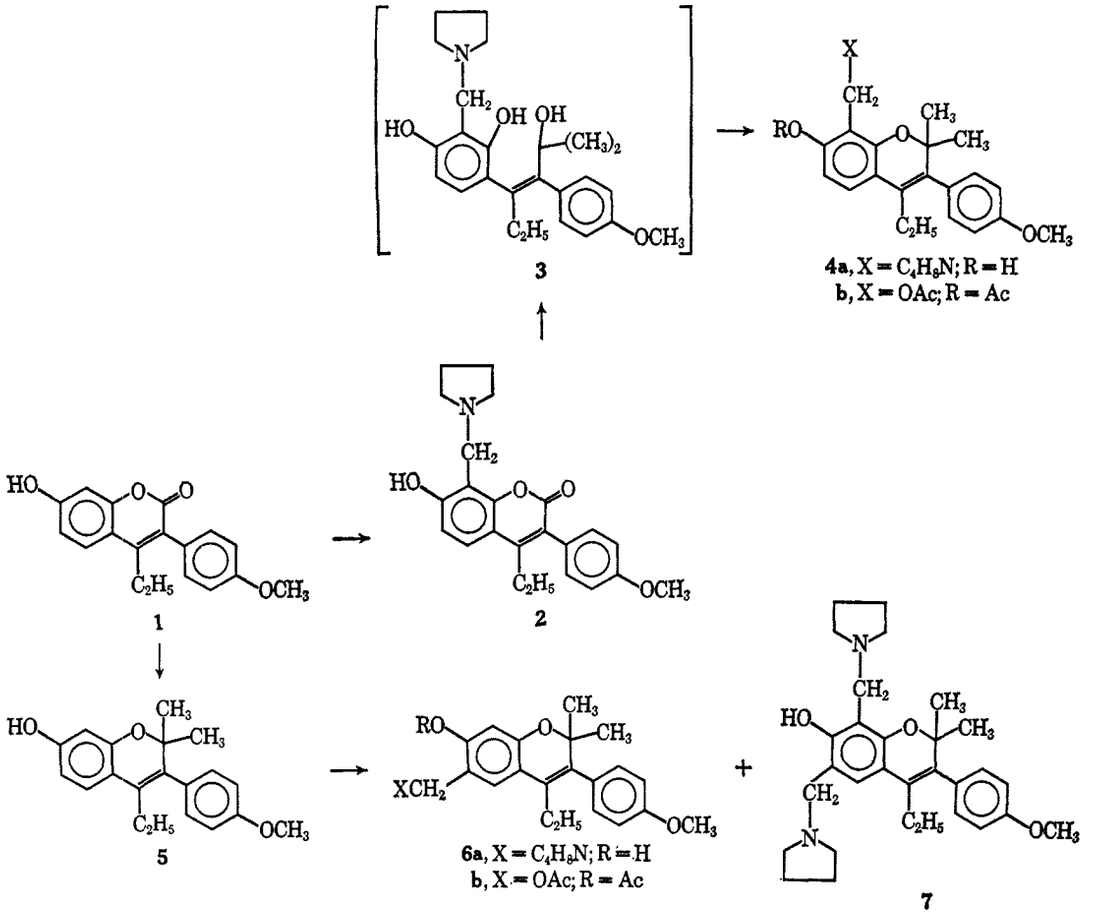
(6) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 88–89.

(7) S. R. Cooper, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 761.

(8) M. Nierenstein and D. A. Clibbens, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 557.

(9) Melting points were taken in capillary tubes (Uni-Melt apparatus) and are uncorrected. Ultraviolet spectra were recorded in methanol on a Bausch and Lomb Spectronic 505. Microanalyses were by Micro-Tech Laboratories, Skokie, Ill.

SCHEME I



stitution).[10] The ultraviolet spectrum showed λ_{max} (ϵ) 223 (27,600), 284 (12,300), and 308 mμ (9930).

2,2-Dimethyl-4'-methoxy-4-ethyl-6-(N-pyrrolidino)methyl-7-hydroxyisoflav-3-ene (6a).—A solution of 14 g (45.0 mmol) of 2,2-dimethyl-4'-methoxy-4-ethyl-7-hydroxyisoflav-3-ene (**5**)[3] in 560 ml of absolute ethanol was treated with pyrrolidine (9.0 ml) and formalin (7.5 ml of 37% solution), refluxed for 45 min (later tlc showed the reaction was over in 1 min), and evaporated almost to dryness at reduced pressure. The residue was stirred with 50 ml of methanol, filtered, washed with two 24-ml portions of methanol, and recrystallized three times from acetone (10 ml/g) to yield a total of 7.62 g (43%): mp 159–161°; mmp with **4a** 132–149°; λ_{max} (ϵ) 225 (32,200), 278 (10,500), 283 (10,660), 310 mμ (11,000).

Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.34; H, 8.05; N, 3.73.

2,2-Dimethyl-4'-methoxy-4-ethyl-7-hydroxy-6,8-bis(N-pyrrolidinomethyl)isoflav-3-ene (7).—The above reaction was repeated with 22.7 g (73 mmol) of **5**, 14.6 ml of pyrrolidine, and 12.2 ml of formaldehyde solution. The solution was refluxed for only 5 min, but, during the evaporation of the ethanol, the bath temperature was inadvertently kept above 60°. Stirring the residue with 81 ml of methanol followed by filtration yielded 7.1 g of impure **6a**, which after recrystallization from methanol had mp 158–159°. When the methanol mother liquor from **6a** was partially evaporated and treated with a little N,N-dimethylformamide and water, crystallization occurred. After recrystallization from acetone the product (**7**) weighed 9 g (26%) and had mp 153.5–154.5°, mmp with **6a** 134°, mmp with **4a** 129–132°. Passage of 1 g in benzene through a 2-g column of Florisil followed by crystallization from acetone gave the analytical sample: mp 153.5–155°; λ_{max} (ϵ) 229 (24,500), 285 (9070), 317 mμ (8500). Integration of the nmr spectrum showed the peaks at δ 1.80 and 2.65 (NC_4H_8) to have twice the relative intensity of those in compounds **4a** and **6a**, and there were two peaks for N-CH_2Ar at δ 3.70 and 3.92.

(10) K. Naskanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., and Nankodo Co., Ltd., Tokyo, 1962, p 27.

Anal. Calcd for $C_{30}H_{40}O_3N_2$: C, 75.59; H, 8.46; N, 5.88. Found: C, 75.74; H, 8.63; N, 6.30.

2,2-Dimethyl-4'-methoxy-4-ethyl-6-acetoxymethyl-7-acetoxyisoflav-3-ene (6b).—Compound **6a** (250 mg, 0.64 mmol) was refluxed for 2 hr with 4 ml of acetic anhydride and 0.25 g of anhydrous sodium acetate.[4a] The mixture was poured onto crushed ice and stirred until a solid was obtained. Purification by crystallization from methanol (20 ml/g), passage of a benzene solution through a short column of Florisil, and three more recrystallizations from methanol yielded **6b** (60%): mp 133.5–134.5°; $\nu_{max}^{CS_2}$ 1740, 1770 cm^{-1}; λ_{max} (ϵ) 229 (37,200), 274 (10,100), 310 mμ (8350).

Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.67; H, 6.69.

2,2-Dimethyl-4'-methoxy-4-ethyl-7-acetoxy-8-acetoxymethylisoflav-3-ene (4b).—Compound **4a** (250 mg, 0.64 mmol) was converted into **4b** by the above method. The crude product obtained by pouring the reaction mixture onto ice was extracted with benzene. The benzene solution was washed with water and sodium bicarbonate solution, dried, and passed through 0.5 g of Florisil to yield 222 mg (82%) of **4b**. Two recrystallizations from methanol gave the analytical sample: mp 102.5–103.5°; $\nu_{max}^{CS_2}$ 1770, 1740 cm^{-1}; λ_{max} (ϵ) 225 (29,900), 272 (10,500), 311 mμ (9090).

Anal. Calcd for $C_{25}H_{28}O_6$: C, 70.74; H, 6.65. Found: C, 70.41; H, 6.39.

Nmr Spectra.—In addition to the aromatic region (see discussion), the rest of the isoflavene nmr spectra were consistent with the assigned structures. In all the compounds the ethyl group appeared as a triplet and quartet (often obscured) at 57 and 131, the *gem*-dimethyl group at 78–82, and the methoxyl at 230 cps. In **4a**, **6a**, and **7** the α- and β-pyrrolidine protons appeared at 158 and 110, and the acetyl methyls of **4b** and **6b** were at 138 (aromatic acetate) and 123 cps (aliphatic acetate). The hydrogen-bonded hydroxyl of **4a** was a sharp singlet at 652, which shifted to 614 in **6a** and appeared as a broadened singlet at 645 cps in **7**. The shielding of the benzylic methylene was dependent upon its position; it was more shielded in the 6 position. Thus it came at 312 cps in **4b** *vs.* 303 in **6b** and at 237

in **4a** *vs.* 227 in **6a**. In the bis derivative **7** there were two peaks at 221 and 235 cps.

Registry No.—**2**, 16797-56-1; **4a**, 16797-57-2; **4b**, 16797-59-4; **6a**, 16797-60-7; **6b**, 16797-61-8; **7**, 16797-62-9.

Acknowledgment.—We thank Frances Holton for experimental assistance in part of this work.

Derivatives of Morphine. VI.[1] The Structure of Dihydrodesoxycodeine E, the Product of Electrolytic Reduction of 14-Bromocodeinone

ULRICH WEISS,[2] THOMAS RÜLL,[3] AND ROBERT B. BRADLEY[2]

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland

Received March 1, 1968

Through electrolytic reduction of 14-bromocodeinone (I) in 25% sulfuric acid, Speyer and Sarre[4] prepared a phenolic dihydrodesoxycodeine (II), $C_{18}H_{23}NO_2 \cdot 0.5C_2H_5OH$, mp 139–140° dec. Their results were subsequently confirmed by Small and Cohen,[5] who proposed the name "dihydrodesoxycodeine E" to distinguish the substance from the several other known dihydrodesoxycodeines. Since II is reduced catalytically (Pd), with uptake of 1 mol of hydrogen, to the well-known tetrahydrodesoxycodeine (III), it must be one of the four possible analogs of III with a double bond in ring C (Scheme I). Of these, the Δ^5 and Δ^6 isomers are known compounds,[6] the dihydrodesoxycodeines C and B, respectively. Both are different from II, which must thus have its double bond in Δ^7 (IIb) or $\Delta^{8(14)}$ (IIa). No evidence on this point appears in the published literature, but the two possibilities should be readily distinguishable by nmr spectroscopy.

Colorless, well-crystallized preparations of II, obtained from a strongly discolored authentic sample[7] still remaining from the work of Small and Cohen[5] by recrystallization from a variety of solvents or by vacuum sublimation, and a new sample isolated by alumina chromatography from a crude product prepared recently by the method of Speyer and Sarre,[4] all showed a triplet (1 H) centered around δ ~5.7 in their nmr spectra. This triplet is very similar to that occurring at δ 5.5[8,9] in the spectrum of neopine (IV) as the X part of a deceptively simple ABX system,[8] and definitely caused by the proton at C-8. As expected, similar signals appear in the spectra of other $\Delta^{8(14)}$ compounds, such as isoneopine (V, triplet, δ 5.5),[9] desoxycodeine D ("desoxyneopine")[10] (VI, triplet, δ 5.5),[11] and neopine methyl ether[12] (VII, quartet, δ 5.45).[11]

The material available at present thus unquestionably has formula IIa rather than IIb. However, even our best samples, though homogeneous on gas chromatography, gave low, very unsharp melting points instead of mp 139–140° given in the literature. Unequivocal proof was thus needed that the substance is chemically identical with the one prepared long ago.[4,5] This proof was furnished by the complete agreement of the melting points of the methiodide and methyl ether methiodide, prepared from one of our samples, with literature values.[4] The nmr spectrum of II methiodide again showed a triplet (1 H) in the olefinic region, this time centered at δ 6.25, and analogous to signals in the spectra of the methiodides of VI[10] and VII[12] (triplets at δ 6.3 and 6.1, respectively).

These findings prove conclusively that II is indeed the $\Delta^{8(14)}$ isomer IIa. The discrepancy between the melting points found by us for II, and those recorded in the literature, appears to be based on polymorphism rather than variable solvation, since it persists after sublimation.

II is thus formed from I by removal of the carbonyl oxygen, reductive opening of the oxygen bridge, and hydrogenolysis of the bromine with allylic shift of the double bond. The last one of these changes is formally identical with that taking place during the *catalytic* (Pd on C in chloroform) reduction[13] of I to neopinone (VIII). The conversion of I to II might conceivably consist of an analogous process, accompanied by the removal of the carbonyl oxygen and opening of the ether bridge. The two processes may or may not be totally concerted; however, no information on the actual mechanism of the electrolytic process is available.

Experimental Section

Nmr spectra were taken on a Varian A-60 instrument in $CDCl_3$ with TMS as internal standard.

Dihydrodesoxycodeine E (IIa).—Both the original, brown sample and the colorless, well-crystallized (rhombic leaflets) preparations obtained from it by vacuum sublimation or recrystallization from ethanol, benzene, or ether, showed very unsharp melting points from about 90° to about 110–115° if taken on a Kofler hot stage. In capillaries, partial melting took place from ~100° up, the last crystals disappearing only at ~140°. Vapor phase chromatograms of the purified samples showed only one peak, retention time 3.55 min (3% OV-17 on Gas Chrom Q mesh 80; column 6 ft × 3 mm, 235°; inlet pressure 26 psi).[14] The old sample showed the same peak accompanied by very small peaks at 4.5 and 8.8 min.

The methiodide (mp 198–199° after recrystallization from ethanol and benzene, lit.[4] mp 199°) and methyl ether methiodide (mp 238–243°, lit.[4] mp 245°) were prepared by the method of Speyer and Sarre.[4] The sample of VI methiodide, left from the work of Small and Mallonee,[10] was labeled "mp 203–204°;" the melting point is given as "204–206° (evacuation tube)" in ref 10. However, the melting point was now found to be ~230° (hot stage); Rapoport and Bonner[15] found 233–234°.

Isolation of II.—The crude mixture of bases resulting from reduction[16] of I by the method of Speyer and Sarre[4] was chro-

(1) Paper V: U. Eisner and U. Weiss, *J. Org. Chem.*, **33**, 1264 (1968).

(2) Laboratory of Physical Biology, National Institute of Arthritis and Metabolic Diseases, Bethesda, Md. 20014.

(3) Laboratoire de Chimie Organique des Hormones, Collège de France, Paris 5e, France.

(4) E. Speyer and K. Sarre, *Ber.*, **57**, 1404 (1924).

(5) L. F. Small and F. L. Cohen, *J. Amer. Chem. Soc.*, **53**, 2227 (1931).

(6) *Cf.* K. W. Bentley, "The Chemistry of the Morphine Alkaloids," Clarendon Press, Oxford, 1954, p 155, and literature quoted there.

(7) This sample and those of several reference compounds were made available from the collection of the late Dr. L. F. Small through the courtesy of Drs. E. L. May and L. S. Sargent.

(8) T. Rüll, *Bull. Soc. Chim. Fr.*, 586 (1963).

(9) S. Okuda, S. Yamaguchi, Y. Kawazoe, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **12**, 104 (1964); T. J. Batterham, K. H. Bell, and U. Weiss, *Aust. J. Chem.*, **18**, 1799 (1965).

(10) L. Small and J. E. Mallonee, *J. Org. Chem.*, **5**, 192 (1940).

(11) Unpublished observations.

(12) L. F. Small, *ibid.*, **20**, 953 (1955).

(13) H. Conroy, *J. Amer. Chem. Soc.*, **77**, 5960 (1955).

(14) The authors are indebted to Mrs. P. F. Highet for the gas chromatograms.

(15) H. Rapoport and M. Bonner, *ibid.*, **73**, 2872 (1951).

(16) The authors are much indebted to Mlle. G. Chalier, Grenoble, France, for performing this electrolytic reduction.