appear as medium or strong bands within the 1445–1460 cm.$^{-1}$ range. In the aliphatic types this is the sole band in this region. Also the benzaldehyde and naphthaldehyde derivatives show but one band (at 1458 cm.$^{-1}$) in this region. The pyridine derivative shows three clearly resolved bands at 1471, 1452, 2435 cm.$^{-1}$ in carbon tetrachloride. The carbon-oxygen stretching vibration associated with the morpholine ring occurs at 1120 ± 10 cm.$^{-1}$.

The absorption band in the 865 cm.$^{-1}$ region previously[1] correlated with the carbon-hydrogen out of plane deformation of the H—C=N grouping is also regularly present in this series of compounds. It appears in all of the morpholine derivatives within a narrow (±2 cm.$^{-1}$) range regardless of solvent or medium used. The previously noted and unassigned strong band in the 990–1010 cm.$^{-1}$ region is also present in the morpholine derivatives. This is one of the strongest bands in the entire spectrum and only the carbon-nitrogen (1610 cm.$^{-1}$) and the carbon-oxygen (1120 cm.$^{-1}$) stretching vibration are of comparable or greater intensity. Only in the heptylidene derivative is this band of decreased intensity.

Initial data[8] on the evaluation of these materials in tumor growth retardation studies have shown that 4-(2′-methoxybenzylideneamino)-morpholine has a ±, − rating at a dose level of 500 mg./kg. and a − rating at a dose level of 125 mg./kg. in tests on experimental mouse sarcoma 180. These results do not establish either a strong or consistent activity. Other compounds in the series, including the pyridinecarboxaldehyde derivatives, which gave dimethylhydrazones of some interest, showed no evidence of tumor growth retardation. Further testing and study of related structures is in progress.

EXPERIMENTAL[9]

Details of typical preparations are given. Data for other compounds are given in the Table. The aldehydes and morpholine were obtained from commercial sources. Products from 2,4-dimethoxybenzaldehyde (m.p. 105°) and from thiophene-2-carboxaldehyde (m.p. 93°) were unstable solids which analyzed low for nitrogen as did also the *p*-nitrobenzaldehyde derivative (m.p. 153°).

4-Aminomorpholine. One hundred and sixty one grams (0.113 mole) of a 5.25% commercial solution of sodium hypochlorite was cooled to 0–2° and this temperature maintained as 13.4 ml. (0.226 mole) of concentrated ammonium hydroxide was poured in slowly with gentle swirling. After standing in an ice bath for 5 min., 11.5 grams, (0.113 mole) of morpholine was added at once. This solution was then allowed to warm slowly to room temperature over a period of 6 hr. with occasional swirling. The solution was filtered to separate a small amount (ca. 0.25 g.) of 4,4′-azomorpholine, m.p. 151°.

4-(2′-Methoxybenzylideneamino)morpholine. The aqueous solution of 4-aminomorpholine, prepared as described in the preceding paragraph, was concentrated to 100 ml. on a steam bath under reduced pressure. One hundred ml. of methanol were then added and after standing 15 min. the solution was filtered to remove precipitated sodium chloride. To this filtrate was then added 7.68 g. (0.0565 mole) of o-methoxybenzaldehyde and the mixture was refluxed for 2 hr. After standing overnight, the white, crystalline product was collected. Recrystallization from ethanol gave 11.9 g., 95.7% of the theoretical yield, of the product as colorless plates, m.p. 76–77°.

4-(2′-Ethylbutylideneamino)morpholine. Twice the quantity (0.226 mol.) of a solution of 4-aminomorpholine prepared as described above was acidified with concentrated hydrochloric acid to the point at which the solution turns from colorless to bright yellow. Ten grams (0.1 mol.) of the 2-ethylbutanal was then added and the mixture refluxed vigorously for 2 hr. After standing overnight and extraction with 100 ml. of ether, the solution was made strongly basic with concentrated ammonium hydroxide and extracted twice again with 100 ml. of ether. The ether extracts of the alkaline solution were combined, dried over anhydrous magnesium sulfate, and evaporated to remove the ether. The residue was distilled to give 7.65 g., 41.6% of the theoretical amount, of product b.p. 69°/1 mm. n_D = 1.4746/25°.

Infrared spectra were determined using a Baird double beam recording spectrophotometer with sodium chloride optics. All measurements were calibrated against the 3.419 μ band for polystyrene and were run at approximately 5% concentrations in spectral grade chloroform.

Acknowledgment. The authors wish to acknowledge support of this research through grant C-2457 from the National Cancer Institute of the United States Public Health Service.

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(8) The authors are indebted to Drs. C. C. Stock, D. A. Clarke, and R. K. Barclay, Sloan-Kettering Institute, for conducting these tests. The procedure and rating scales are given in Cancer Research, Suppl. No. 1, p. 91 (1953) and Suppl. No. 2, p. 179 (1955).

(9) Analyses by Micro-Tech Laboratories, Skokie, Illinois.

Plant Polyphenols. X. 7- and 4′-*O*-Methylcoumestrol

LEONARD JURD[1]

Received April 28, 1959

Coumestrol (I R = R_1 = H), recently isolated from a large number of legume forages by Bickoff, Booth, and their associates, has been shown to be a potent and potentially valuable estrogen.[2–5] Since 4′,7-di-*O*-methylcoumestrol possesses only about 1/4 the estrogenic activity of coumestrol[6] it was of some importance to prepare and quantitatively bio-assay the 7- (I R = Me; R_1 = H) and 4′- (I R = H; R_1 = Me) mono-*O*-methyl derivatives in order to determine the contribution of each of the hydroxyl

(1) Financial support for this work was provided by the Diamond Walnut Growers, Inc., Stockton, Calif.

(2) E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson, and G. O. Kohler, *J. Agr. Food Chem.*, 6 (7), 536 (1958).

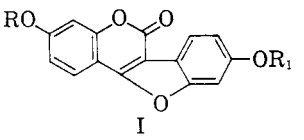
(3) E. M. Bickoff, A. N. Booth, R. L. Lyman, A. L. Livingston, C. R. Thompson, and F. DeEds, *Science*, **126**, 969 (1957).

(4) E. M. Bickoff, R. L. Lyman, A. L. Livington, and A. N. Booth, *J. Am. Chem. Soc.*, **80**, 3969 (1958).

(5) O. H. Emerson and E. M. Bickoff, *J. Am. Chem. Soc.*, **80**, 4381 (1958).

(6) E. M. Bickoff, private communication.

groups to the estrogenic activity of the 3-phenyl-4-hydroxycoumarin nucleus. Attempts to prepare these monomethyl compounds by the direct methylation of coumestrol, however, were not satisfactory.[6] At the kind invitation of E. M. Bickoff, therefore, these new monomethyl derivatives have now been prepared by the selective alkylation of coumestrol diacetate, a technique which was recently employed in the preparation of partial ethers of polyhydroxyflavones.[7,8]



I

In coumestrol the 7-hydroxyl, being conjugated with the lactone carbonyl group, is strongly acidic. In confirmation of this the long wave length band of coumestrol (λmax 343 mμ) is shifted to 387 mμ in sodium ethylate but only to 362 mμ in sodium acetate (Table I), indicating that of the two hydroxyl groups of coumestrol only one is sufficiently acidic to be ionized by the weakly basic sodium acetate and this is probably the 7-hydroxyl. On this basis it would be anticipated that alkylation of coumestrol diacetate would result in the selective replacement of the 7-acetoxyl group only. In agreement with this it has been found that coumestrol diacetate reacts with excess of methyl iodide, potassium carbonate in acetone to give 7-*O*-methylcoumestrol monoacetate. On acid hydrolysis this gives 7-*O*-methylcoumestrol, m.p. 274°, the ultraviolet spectrum of which is unaffected on the addition of sodium acetate (Table I). Benzylation of coumestrol diacetate under similar conditions gives 7-*O*-benzylcoumestrol monoacetate. Hydrolysis of this gives 7-*O*-benzylcoumestrol, m.p. 211°, which is methylated to form (I R = $C_6H_5CH_2$—; R_1 = Me). Debenzylation of the latter compound then gives 4′-*O*-methylcoumestrol, m.p. 337°. The ultraviolet spectrum of this ether in sodium acetate has a peak at 362 mμ due to ionization of the 7-hydroxyl and a peak at 377 mμ indicating partial opening of the lactone ring.

Preliminary data on the bio-assay of these monoalkyl ethers has indicated that they are estrogenic although less than $^1/_3$ as active as the parent compound. The 4′-*O*-methyl derivative is more active than either the 7-*O*-methyl- or 7-*O*-benzyl compounds.[6]

TABLE I

ULTRAVIOLET SPECTRA OF COUMESTROL DERIVATIVES

Compound	λ max, mμ EtOH	EtOH–NaOAc	0.002*M* NaOEt
Coumestrol	343	362	387
	304	312	321
	244	264[a]	281
		243	260[a]
7-*O*-methylcoumestrol	342	342	380
	303	303	318
	243	243	270
7-*O*-benzylcoumestrol	343	343	380
	303	304	318
	244	244	271
4′-*O*-methylcoumestrol	341	377	377
	303	362	
	243	311	311
		303	
		265	266
		243	243
4′-*O*-methyl-7-*O*-benzylcoumestrol	341		
	303		
	243		
Coumestrol diacetate	342		
	327		
	297		
	236		
7-*O*-methylcoumestrol acetate	348		
	333		
	299		
	240		
7-*O*-benzylcoumestrol acetate	348		
	333		
	298		
	240		
4′-*O*-methylcoumestrol acetate	337		
	302		
	243		

[a] Inflection.

EXPERIMENTAL

7-O-Methylcoumestrol. A mixture of coumestrol diacetate (2.0 g.), methyl iodide (30.0 ml.), anhydrous potassium carbonate (12.0 g.) and acetone (140 ml.) was heated under reflux for 32 hr. The filtered acetone solution was concentrated to small volume and diluted with ethanol. A colorless crystalline solid (1.75 g.) separated. It was collected and recrystallized from acetone-methanol. The 7-*O*-methylcoumestrol acetate thus obtained separated in colorless needles, m.p. 204–206°.

Anal. Calcd. for $C_{18}H_{12}O_6$: C, 66.7; H, 3.73; 1 MeO—, 9.63. Found: C, 66.5; H, 3.87; MeO—, 9.26.

15% Aqueous hydrochloric acid (30 ml.) was added to a solution of the above product (1.7 g.) in acetone (100 ml.) and ethanol (80 ml.). The volume of the solution was reduced to about 50 ml. by heating on a steam bath during 1.5 hr. Water (50 ml.) was added and the solid was collected and recrystallized from acetone-methanol. Chromatography of this product on a silicic acid chromatostrip showed the presence of a small quantity of coumestrol. The crystalline product was, therefore, suspended in dilute aqueous potassium carbonate. The undissolved 7-*O*-methyl compound was collected and recrystallized from acetone-methanol. 7-*O*-Methylcoumestrol was thereby obtained in slightly yellow needles, m.p. 274° (0.8 g.).

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.1; H, 3.83; 1 MeO—, 11.0. Found: C, 68.2; H, 3.63; MeO—, 11.0.

The pure 7-*O*-methylcoumestrol (0.1 g.) was reacetylated by heating it with acetic anhydride and fused sodium acetate for 1 min. Water was added, the solid was collected and crystallized from acetone-ethanol. The pure 7-*O*-methylcoumestrol acetate separated in colorless glistening needles, m.p. 208°.

(7) L. Jurd, *Chem. & Ind. (London)*, 1452 (1957).
(8) L. Jurd, *J. Am. Chem. Soc.*, **80**, 5531 (1958).

Anal. Calcd. for $C_{18}H_{12}O_6$: C, 66.7; H, 3.73; 1 MeO—, 9.63; 1 CH_3CO—, 13.3. Found: C, 66.8; H, 3.82; MeO—, 9.59; CH_3CO—, 13.5.

7-O-Benzylcoumestrol. Coumestrol diacetate (3.0 g.) was refluxed with a mixture of benzyl chloride (30.0 ml.), potassium iodide (4.0 g.), anhydrous potassium carbonate (10.0 g.), and dry acetone (160 ml.) for 20 hr. The filtered acetone solution was evaporated to an oil. Warm hexane (100 ml.) was added, the mixture was cooled, and the crystalline precipitate was collected. It was purified by dissolving it in acetone (500 ml.). The filtered solution was concentrated to about 50 ml. and diluted with methanol (50 ml.). The colorless product (2.8 g.; m.p. 203°) was collected and recrystallized twice more from acetone-methanol. 7-*O*-Benzylcoumestrol acetate separated in colorless fluffy needles, m.p. 205°.

Anal. Calcd. for $C_{24}H_{16}O_6$: C, 72.0; H, 4.03; 1 CH_3CO—, 10.8. Found: C, 72.0; H, 4.09; CH_3CO—, 11.1.

A solution of the above acetate (2.6 g.) in acetone (400 ml.) was treated with ethanol (100 ml.), water (20 ml.), and concentrated hydrochloric acid (20 ml.). The mixture was heated on a steam bath for 1 hr., most of the acetone being allowed to evaporate during this period. Crystallization of the product then began. Water (80 ml.) was slowly added and the solid was collected. Recrystallized from acetone-methanol (charcoal), 7-*O*-benzylcoumestrol separated in colorless needles, m.p. 211° (1.8 g.). It dissolved instantly in cold aqueous sodium hydroxide to give a yellow solution.

Anal. Calcd. for $C_{22}H_{14}O_5$: C, 73.7; H, 3.94. Found: C, 73.7; H, 4.02.

Reacetylation of the 7-*O*-benzylcoumestrol gave 7-*O*-benzylcoumestrol acetate, m.p. 205°.

4'-O-Methyl-7-O-benzylcoumestrol. A mixture of the 7-*O*-benzylcoumestrol (1.4 g.), methyl iodide (15.0 ml.), anhydrous potassium carbonate (6.0 g.) and dry acetone (50 ml.) was refluxed for 2.5 hr. The filtered acetone solution was evaporated. The crystalline residue was washed with cold dilute aqueous sodium hydroxide and then recrystallized from acetone-methanol. 4'-*O*-Methyl-7-*O*-benzylcoumestrol was obtained in colorless felted needles, m.p. 187° (1.1 g.).

Anal. Calcd. for $C_{23}H_{16}O_5$: C, 74.2; H, 4.33; 1 MeO—, 8.39. Found:C, 74.2; H, 4.39; MeO—, 8.23.

4'-O-Methylcoumestrol. A solution of the 4'-*O*-methyl-7-*O*-benzylcoumestrol (1.0 g.) in glacial acetic acid (200 ml.) and concentrated hydrochloric acid (100 ml.) was heated on a steam bath for 15 min. Water (500 ml.) was added and the precipitated ether was collected. Recrystallized from acetone, 4'-*O*-methylcoumestrol separated in colorless needles, m.p. 337° (0.55 g.).

Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.1; H, 3.83; MeO—, 11.0. Found: C, 68.3; H, 3.77; MeO—, 10.7.

The 4'-*O*-methylcoumestrol was acetylated by boiling it with acetic anhydride and sodium acetate for 1 min. 4'-*O*-methylcoumestrol acetate crystallized from acetone-methanol in colorless needles, m.p. 240° (with sintering at 234°).

Anal. Calcd. for $C_{18}H_{12}O_6$: C, 66.7; H, 3.73; 1 MeO—, 9.63; 1 CH_3CO—, 13.3. Found: C, 66.9; H, 3.89; MeO—, 9.58; CH_3CO—, 13.3.

Acknowledgment. The author is indebted to E. M. Bickhoff for the generous gift of coumestrol diacetate and to L. M. White for the elementary analyses.

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Some Urethans Derived from 3-Amino-1-propanol[1]

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Received April 30, 1959

Previous publications[2,3] have shown that 3-amino-1-propanol and ethylene carbonate are convenient starting materials for preparing the cyclic urethan tetrahydro-2*H*-1,3-oxazin-2-one, now known[4,5] to be convertible to a polyurethan. In the course of a restudy[6] of the preparation and polymerization of this cyclic urethan, several hitherto unreported derivatives of 3-amino-1-propanol were prepared.

The immediate product from the reaction of 3-amino-1-propanol with ethylene carbonate at a temperature below 50° is a viscous liquid, identified by Delaby and coworkers[3] as 2-(hydroxyethyl)-*N*-3'-(hydroxypropyl)-urethan (I). The yield of this product, not given by previous workers,[2,3] was shown to be practically quantitative by conversion to the dicarbanilate (VI). Heating the viscous liquid gives the cyclic urethan (II).

Another route to the cyclic urethan involved *N*-3-hydroxypropyl-*N'*-phenylurea (III), which was obtained by the reaction of 3-amino-1-propanol with phenyl isocyanate under mild conditions. The urea (III) was converted to the urethan (II) by applying Weickmann's method of ring closure.[7] The structure of the urea (III) was indicated by its amide carbonyl absorption at 1625 cm.$^{-1}$ and at 1541–1600 cm.$^{-1}$ with the absence of absorption characteristic of the urethan carbonyl. By treatment of the urea (III) with phenyl isocyanate in the presence of triethylamine, a quantitative yield of the 3-phenylurethan (VII) was obtained. This compound showed urethan carbonyl absorption at 1653 cm.$^{-1}$ in addition to the amide absorption bands of compound (III).

The cyclic urethan (II) gave a γ-phenylallophanate, (V), when treated with phenyl isocyanate during heating.

In agreement with recent work[4,5] and contrary to our previous statement,[2] the cyclic urethan (II) polymerized on heating, to give the polyurethan

(1) From the M.S. thesis of R. E. Read, University of Delaware, 1957.

(2) E. Dyer and H. Scott, *J. Am. Chem. Soc.*, **79**, 672 (1957).

(3) R. Delaby, R. Damiens, and G. d'Huyteza, *Compt. rend.*, **239**, 674 (1954).

(4) E. K. Drechsel, U. S. Patent **2,701,246**, Feb. 1, 1955; *Chem. Abstr.*, **50**, 2686 (1956); and U. S. Patent **2,744,897**, May 8, 1956; *Chem. Abstr.*, **51**, 498 (1957).

(5) H. K. Hall, Jr., and A. K. Schneider, *J. Am. Chem. Soc.*, **80**, 6409 (1958).

(6) The authors were then unaware of the work in ref. (4) and (5).

(7) A. Weickmann, Ger. Patent **858,402**, Dec. 8, 1952; *Chem. Abstr.*, **47**, 11255 (1953).