oil bath at 180° for 8 hr. The product obtained crystallized from dilute alcohol (charcoal) in needles, m.p. 192°.

Anal. Calcd. for $C_{17}H_{10}O_2$: C, 82.9; H, 4.1. Found: C, 83.1; H, 4.6.

Ethyl-2,1-anthra-α-pyrone-3'-carboxylate (IIb). A mixture of 1-formyl-2-anthrol (2.22 g.), diethyl malonate (1.92 g.) and a few drops of piperidine was kept at room temperature for 4 days. The product, which separated on treating the reaction mixture with dilute hydrochloric acid, crystallized from alcohol (charcoal) in yellow needles, m.p. 194°.

Anal. Calcd. for $C_{20}H_{14}O_4$: C, 75.5; H, 4.4. Found: C, 75.3; H, 4.6.

2,1-Anthra-α-pyrone-3'-carboxylic acid (IIc). Obtained on alkaline hydrolysis of the above ester was first crystallized from dilute alcohol and then from benzene in fine red needles, m.p. 305–306° (dec.).

Anal. Calcd. for $C_{18}H_{10}O_4$: C, 74.5; H, 3.5. Found: C, 74.7; H, 3.7.

The acid on decarboxylation in quinoline solution with copper powder gave 2,1-anthra-α-pyrone described above.

1-Acetyl-2-anthrol. 2-Anthrol (1.9 g.) and acetic anhydride (1.3 g.) in nitrobenzene (30 ml.) was mixed with a solution of anhydrous aluminium chloride (2.7 g.) in nitrobenzene (20 ml.), and the reaction mixture, protected from moisture, was kept for 72 hr. at room temperature. It was then treated with ice and hydrochloric acid, and the nitrobenzene steam-distilled. The product obtained was extracted with alkali, and the alkaline extract acidified with hydrochloric acid. The precipitated solid crystallized from dilute alcohol (charcoal) in yellow needles, m.p. 112–113°. (Jain and Seshadri[4] who prepared it by the Fries migration of 2-anthrolacetate at higher temperature give m.p. 219°). It gave a bluish coloration with alcoholic ferric chloride, which turned green on keeping.

Anal. Calcd. for $C_{16}H_{12}O_2$: C, 81.4; H, 5.1. Found: C, 81.3; H, 5.2.

The same product was obtained in inferior yield (i) on heating the above reaction mixture on a steam bath for 2 hr. and (ii) in the Fries rearrangement of 2-anthrolacetate in nitrobenzene by keeping for 24 hr. at room temperature.

The *2,4-dinitrophenylhydrazone* prepared as usual crystallized from acetic acid, m.p. 235°.

Anal. Calcd. for $C_{22}H_{16}O_5N_4$: N, 13.5. Found: N, 14.1.

The *methyl ether* crystallized from dilute alcohol in small yellowish plates, m.p. 99°.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.6; H, 5.6. Found: C, 82.0; H, 5.7.

On sodium hypochlorite oxidation at 85° it gave a product which crystallized from acetic acid in small yellow needles, m.p. and mixed m.p. with 2-methoxyanthraquinone-1-carboxylic acid, prepared according to Ch. Marschalk[2] was 276–277°.

2'-Methyl-3'-acetyl-2,1-anthra-γ-pyrone (Ic). 1-Acetyl-2-anthrol (1 g.) was heated with freshly fused sodium acetate (3 g.) and acetic anhydride (6 ml.) in an oil bath at 180° for 8 hr. The product obtained on working up the reaction mixture crystallized from acetic acid (charcoal) in yellow needles m.p. 252–253°.

Anal. Calcd. for $C_{20}H_{14}O_3$: C, 79.5; H, 4.6. Found: C, 79.6; H, 4.9.

The above γ-pyrone (0.5 g.) in alcohol (50%, 50 ml.) when refluxed with sodium carbonate (2 g.) for 2 hr. gave the deacetylated product, which crystallized from dilute acetic acid in needles, m.p. and mixed m.p. with 2'-methyl-2,1-anthra-γ-pyrone, described above, was 173°.

2'-Phenyl-3'-benzoyl-2,1-anthra-γ-pyrone (Id). 1-Acetyl-2-anthrol (1 g.) was heated with freshly fused sodium benzoate (1.5 g.) and benzoic anhydride (5 g.) in an oil bath at 180° for 8 hr. The reaction mixture was then treated repeatedly with hot water and sodium bicarbonate solution. The residue crystallized from acetic acid in small yellow needles, m.p. 270°.

Anal. Calcd. for $C_{30}H_{18}O_3$: C, 84.5; H, 4.2. Found: C, 84.1; H, 4.2.

The above γ-pyrone (0.2 g.) was refluxed with alcoholic sodium hydroxide (5%, 20 ml.) on a steam bath for 1 hr. and the product obtained crystallized from dilute acetic acid in pale yellow needles. M.p. and mixed m.p. with 2'-phenyl-2,1-anthra-γ-pyrone described above was 219°.

Ethyl-1-formyl-2-anthroxyacetate. 1-Formyl-2-anthrol (0.5 g.) was dissolved in dry acetone (50 ml.) and refluxed on a steam bath with ethyl bromoacetate (0.5 ml.) and anhydrous potassium carbonate (3 g.) for 3 hr. The product obtained on working up the reaction mixture crystallized from alcohol (charcoal) in yellow needles, m.p. 140°.

Anal. Calcd. for $C_{19}H_{16}O_4$: C, 74.0; H, 5.2. Found: C, 73.9; H, 5.1.

1-Formyl-2-anthroxyacetic acid obtained on alkaline hydrolysis of the above ester, crystallized from dilute acetone (charcoal) in reddish yellow needles, m.p. 222–223°.

Anal. Calcd. for $C_{17}H_{12}O_4$: C, 72.8; H, 4.3. Found: C, 72.4; H, 4.2.

Anthra[2,1-b]furan (IIIa). The above acid (0.1 g.), acetic anhydride (2 ml.) and freshly fused sodium acetate (0.3 g.) was boiled for 30 min. The product, which separated on addition of water, crystallized from dilute acetic acid (charcoal) in greenish yellow plates, m.p. 177–178°.

Anal. Calcd. for $C_{16}H_{10}O$: C, 88.1; H, 4.6. Found: C, 88.1; H, 4.7.

Ethyl-1-acetyl-2-anthroxyacetate was obtained from 1-acetyl-2-anthrol and ethyl bromoacetate. It crystallized from alcohol (charcoal) in greenish yellow needles, m.p. 127–128°.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6. Found: C, 74.7; H, 5.7.

1-Acetyl-2-anthroxyacetic acid was obtained on alkaline hydrolysis of the above ester. It crystallized from dilute acetic acid in greenish yellow needles, m.p. 190°.

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.5; H, 4.8. Found: C, 73.5; H, 4.4.

1-Methylanthra[2,1-b]furan (IIIb) was obtained on cyclization of the above acid with acetic anhydride and fused sodium acetate. It crystallized first from dilute acetic acid (charcoal) and then from alcohol in needles, m.p. 139–140°.

Anal. Calcd. for $C_{17}H_{12}O$: C, 87.9; H, 5.2. Found: C, 87.5; H, 5.4.

CHEMISTRY DEPARTMENT
M.S. UNIVERSITY OF BARODA
BARODA, INDIA

Alkylidene- and Arylideneaminomorpholines

RICHARD H. WILEY, H. KEITH WHITE, AND GETHER IRICK

Received April 27, 1959

A study of the dimethylhydrazones described recently[1] as of interest as isosteres of 3,3-dimethyl-1-phenyltriazene in tumor growth retardation studies disclosed a border line activity in some derivatives and prompted the study of additional related hydrazones. This report describes the preparation, infrared absorption characteristics, and preliminary evaluation of the 4-aminomorpholine derivatives (III) of some of the alkyl and aromatic aldehydes which, as dimethylhydrazones, showed such activity. The only previously known compounds of this

(1) Richard H. Wiley, S. C. Slaymaker, and H. Kraus, *J. Org. Chem.*, 204 (1957).

type are the benzaldehyde derivative[2] and the *o*-, *m*-, and *p*-hydroxy-; *o*- and *m*-nitro-; 3-methoxy-4-hydroxy-; and 3,4-methylenedioxy-substituted benzaldehyde[3] derivatives.

The 4-aminomorpholine (II) used in our studies was prepared by the chloramine amination of morpholine (I)[4,5,6,7] and used without isolation in the preparation of the derivatives. Our preferred procedure, which is significantly different from the previously defined optimum conditions for chloramine and hydrazine formation, involves the use of a 2:1 mole ratio of ammonia to hypochlorite in the formation of chloramine and reaction of the unisolated chloramine within 5 min. with an equimolar quantity of morpholine. This solution was concentrated to about one half its volume, diluted with methanol to precipitate sodium chloride, and then reacted with .5 mol. of the aldehyde. Yields based on the aldehyde used are given in Table I. The previously defined optimum conditions for hydrazine formation[4,5,6,7] specify a 3:1 mole ratio of ammonia to hypochlorite, a much longer time (1.5 hr.) for completion of the chloramine formation, and a 6:1 mol. ratio of amine to chloramine. We prefer the lower ratio of ammonia to hypochlorite to avoid the presence of increased quantities of ammonia to be neutralized prior to addition of the aliphatic aldehydes. The use of a short (5 min.) hypochlorite ammonia reaction time is based on the observation[7] that for 2:1 ammonia to hypochlorite ratio the slope of the chloramine decomposition curve shows a very high initial decomposition rate and extrapolates to an initial yield of over 90%. We prefer the lower (1:1) ratio of amine to chloramine in the hydrazine formation to avoid the separation problems arising from use of a larger excess of amine. In order to overcome the decrease in yield resulting from use of this lower ratio we have used more concentrated reagents and lengthened the reaction time from 2 to 6 hr. In favorable examples, such as with 2-methoxybenzaldehyde, using a 2:1 mol. ratio of the unisolated hydrazine thus prepared to the aldehyde we have obtained essentially quantitative yields of the aldehyde hydrazone. This establishes that in these favorable examples, at least, a minimum yield of 50% of the hydrazine was obtained from the chloramine. It is to be noted that these conditions have been defined in terms of a convenient method for preparing carbonyl derivatives and not in terms of absolute maximum yields of hydrazine in the chloramine reaction.

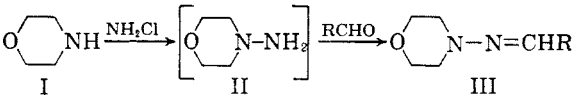
(2) L. Knorr and H. W. Brownsdon, *Ber.*, **35**, 4474 (1902).
(3) L. Dugan and H. M. Haendler, *J. Am. Chem. Soc.*, **64**, 2502 (1942).
(4) L. F. Audrieth and L. H. Diamond, *J. Am. Chem. Soc.*, **76**, 4869 (1954).
(5) L. H. Diamond and L. F. Audrieth, *J. Am. Chem. Soc.*, **77**, 3131 (1955).
(6) R. A. Rowe and L. F. Audrieth, *J. Am. Chem. Soc.*, **78**, 563 (1956).
(7) L. F. Audrieth and R. A. Rowe, *J. Am. Chem. Soc.*, **77**, 4726 (1955).

TABLE I

ALKYLIDENE- AND ARYLIDENEAMINOMORPHOLINES

Carbonyl Compound	Yield (%)	b.p. or m.p.[a]	Nitrogen Analysis Calcd.	Found
3-Methylbutanal	37	b100/9[b]	16.46	16.39
2-Ethylbutanal	42	b69/1[c]	15.20	15.33
1-Heptanal	24	b126/6[d]	14.13	14.31
Benzaldehyde	..	m89EW	14.73	14.69
4-acetamido	77	m206MW	16.99	16.79
4-chloro-	..	m99E	12.47	12.62
3,4-diethoxy-	90	m99MW	10.07	9.80
2-methoxy-	96	m76EW	12.72	12.56
4-dimethylamino-	58	m166EW	18.01	17.82
3-nitro-	90	m153EW	...	...
Naphthaldehyde	67	m63EW	11.66	11.24
2-hydroxy-	73	m121MW	10.93	10.72
9-Anthraldehyde	58	m193EW	9.65	9.50
Pyridine:				
2-carboxaldehyde-	44	m47-56[e]	19.41	19.46[g]
6-methyl-2-carboxaldehyde	35	m53-7[f]	19.00	18.83[g]
2,6-dicarboxaldehyde	32	m136MW	23.09	23.03

[a] b, boiling point in °C./mm; m, melting point. Solids recrystallized from M, methanol; E, ethanol; W, water. [b] n_D^{25} 1.4739. [c] n_D^{25} 1.4746. [d] n_D^{26} 1.4746. [e] b 118/0.15. [f] b 168/1. [g] analysis on dipicrate.



I II III

The infrared absorption data provide additional confirmation for the assignments previously reported for the dimethylhydrazones.[1] The absorption in the 1610 cm.$^{-1}$ region attributable to the C=N stretching vibration is identifiable in the aliphatic types but obscured in the aromatic types. For the three aliphatic aldehyde derivatives where the absorption is clearly attributable to the stretching vibration of the carbon-nitrogen double bond the absorption is at 1614 cm.$^{-1}$ and is relatively weak (in chloroform). For the aromatic aldehydes, in which both carbon-carbon and carbon-nitrogen double bond vibrations occur, there are usually two or three well-defined strong bands in this region. Often the absorption band at 1615 cm.$^{-1}$ is the weaker or weakest and because it is nearly always present and the others, although also usually present, occur at variable positions in differently substituted types, it is probable that this band can be attributed with some confidence to the carbon nitrogen double bond or a contribution therefrom. The pyridine aldehyde derivatives show, as the most intense band in this region, a broad absorption at 1570–1582 cm.$^{-1}$ accompanied by a shoulder or weak band at 1600 cm.$^{-1}$ This probably represents overlap of the ring and side chain carbon-nitrogen double bond vibrations.

The stretching vibrations attributable to the methylene groups appear clearly defined at 2950, 2850, and 1450 cm.$^{-1}$ in spectra determined in chloroform and carbon tetrachloride solutions. The last

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.

LOUISVILLE, KY.

(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.