cerebral stimulation in rats of the order of caffeine when administered subcutaneously. These results were kindly furnished by Dr. G. M. Chen of Parke, Davis and Company Research Laboratories. Also, Dr. D. A. McGinty, of the same laboratories, indicated that compounds 1, 2, and 4 show insufficient diuretic effect in the rat for further interest.

EXPERIMENTAL

7-(Substituted aminomethyl)theophyllines (*Table I*). To a well-stirred mixture of 0.01 mole of theophylline and 4 ml. of alcohol, 0.01 mole of the appropriate amine was added. Then, 0.9 ml. (0.01 mole) of 38% formaldehyde solution was added with stirring while heat was evolved. At this stage, usually the starting materials had dissolved. Any undissolved material was removed by filtration. The filtrate was refrigerated to achieve complete precipitation of the product, which was then collected by filtration and air dried for 72 hr.

7-Chloromethyltheophylline (*A*). A mixture of 8 g. (0.04 mole) of theophylline, 4 ml. (0.048 mole) of 38% formaldehyde solution and 23 ml. of concentrated hydrochloric acid was allowed to stand for 20 min. at room temperature, after which time all the solid had dissolved. Then, a vigorous stream of hydrogen chloride gas was passed into the solution, with the evolution of heat, and maintained until the solution had cooled to room temperature, which required about 30 min. The solution was diluted with ten volumes of acetone and then refrigerated for at least 2 days or until a good yield of white solid had been obtained. It could not be recrystallized without decomposition. Air drying for several days gave 7.7 g. (75% yield) of product, m.p. 257–258° dec. The solid was water soluble and gave a positive halogen test with silver nitrate.

Anal. Calcd. for $C_8H_9ClN_4 \cdot 1\text{-}^1/_2H_2O$: C, 37.58; H, 4.73; Cl, 13.87. Found: C, 37.77; H, 4.73; Cl, 13.86.

(*B*). To 0.2 g. (0.0095 mole) of 7-hydroxymethyltheophylline, 1.5 ml. of thionyl chloride was added slowly at room temperature. The mixture was heated at reflux temperature for 5 min. and then allowed to stand at room temperature for 20 min. Excess thionyl chloride was removed by distillation on the steam bath. Acetone was added to the residue and the mixture was stirred and cooled. The product was removed by filtration and washed well with acetone. The solid was air dried to yield 0.2 g. (82%) of 7-chloromethyltheophylline, m.p. 258–259°.

7-Hydroxymethyltheophylline was prepared from 7-chloromethyltheophylline by recrystallizing the latter from alcohol. The desired product, resulting from a hydrolytic action, was obtained in quantitative yield, m.p. 261–262° dec. Two more recrystallizations from alcohol were carried out without significant change in melting point.

Anal. Calcd. for $C_8H_{10}N_4O_4$: C, 45.71; H, 4.79. Found: C, 45.67; H, 4.88.

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(6) The ready hydrolysis of 7-chloromethyltheophylline to 7-hydroxymethyltheophylline may be explained by a neighboring group effect exhibited by the 6-keto group which, bearing a partial negative charge, would be expected to aid the removal of the chloro group bearing a negative charge. The resulting hydroxymethyltheophylline would be stabilized *via* hydrogen bonding through the same 6-keto group. Also, the instability of the Mannich bases may again be explained by consideration of perturbations at the 6-keto position. A resonance structure bearing a negative charge at the 6-keto and a positive one at the 7-position might be expected to yield the 7-theophylline anion.

Synthesis of a Radioactive Estrogen, 3,4-Dianisyl-2-*t*-3-hexene

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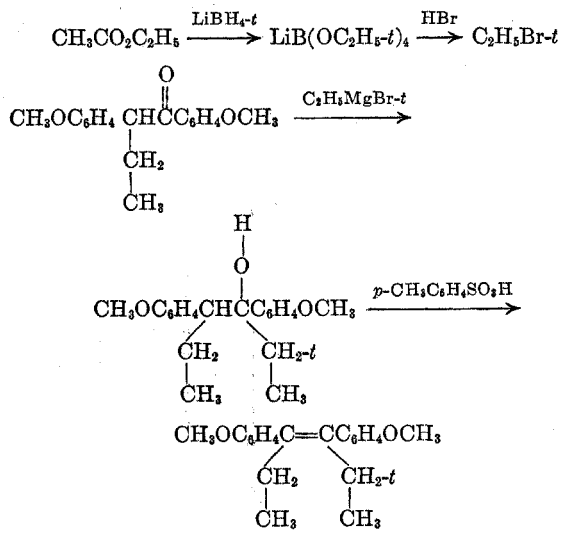
Radioactive 3,4-dianisyl-3-hexene (the dimethyl ether of stilbestrol) was needed recently for feeding experiments with poultry.[1] It was necessary to use tritium as the tagging isotope in spite of the more laborious assays anticipated because of the quantity of estrogen desired. Because the hormone would be greatly dispersed in use, a high initial specific activity was required. Since this compound may be demethylated *in vivo* to stilbestrol, labeling of the compound on the methoxyl groups was undesirable. Hence tritium was incorporated into the molecule by chemical synthesis rather than by recoil[2] or exchange[3] reactions.

The method of synthesis was as follows:



Good weight and radioactivity yields were obtained in each step except the last one. The over-all radioactivity yield based on tritium gas was 3.2%.

EXPERIMENTAL

Preparation of 1-bromo-1-t-ethane. The procedure used was based on one devised by Smith, Wilzbach, and Brown[4] for methyl-*t* iodide. Lithium borohydride (0.1827 g.), obtained from Metal Hydrides, Inc., was contacted with a mixture of 250 mc. of tritium and 23 ml. of hydrogen for 36 hr. at

(1) Results of these experiments will be reported soon by Dr. Rollin Thayer and Mr. Don deSteiguer, Department of Poultry Science, Oklahoma State University. Financial support of this work came from this Department through the Agricultural Experiment Station and the Research Foundation of Oklahoma State University.

(2) (a) R. Wolfgang, F. S. Rowland, and C. N. Turton, *Science*, **121**, 715 (1955); (b) F. S. Rowland and R. Wolfgang, *Nucleonics*, **14**, No. 8, 58 (1956); (c) F. S. Rowland, C. N. Turton, and R. Wolfgang, *J. Am. Chem. Soc.*, **78**, 2354 (1956).

(3) K. Wilzbach, *J. Am. Chem. Soc.*, **79**, 1013 (1957).

200°. All except 8.5% of the tritium wax taken up by the lithium borohydride; the remaining gaseous tritium was converted to tritiated water.[5] Dry tetrahydrofuran (10 ml.) and 1.1890 g. of dry ethyl acetate were distilled into the flask containing tritium-enriched borohydride. The contents of the flask were warmed slowly and kept at reflux temperature for 8 hr. The solvent and a small amount of excess ester was removed by distillation. Twenty-five ml. of hydrobromic acid (Baker's Analyzed Reagent) was added slowly to the flask through a dropping funnel while the reflux condenser was cooled with water. The flask was heated to 90° for 2.5 hr. while a stream of nitrogen was passed through it and then through a trap immersed in liquid nitrogen. When the reaction was complete, the product in the trap was purified on the vacuum line, and only material boiling above −85° and lower than −58° at 1 micron pressure was retained. The vapor pressure of the product at 27° was 494 mm. compared to 475 mm. at 25.5° for a known sample of ethyl bromide. The radioactive ethyl bromide weighed 1.783 g.

Preparation of 3,4-dianisyl-2-t-3-hexene. A Grignard solution was prepared from the above ethyl bromide, 1.102 g. of non-radioactive ethyl bromide, 0.6398 g. of magnesium, and 20 ml. of diethyl ether. A solution of 7.51 g. of α-ethyldesoxyanisoin[6] in 10 ml. of ether was added and the mixture was refluxed. After 2 hr. the reaction flask had an oily layer at the bottom, indicating excess ketone. Another Grignard solution prepared from 5.77 g. of ethyl bromide and 1.50 g. of magnesium was added to the flask to insure complete reaction of the ketone. The mixture was hydrolyzed in acidified water and ice and worked up in the usual way.[7] A white solid weighing 6.07 g. and melting at 75–95° was obtained. Two forms of 3,4-dianisyl-3-hexanol have been reported,[8] one melting at 114–117° and one at 83–85.5°; the solid product was assumed to be a mixture of these two forms.

This mixture was dehydrated by the method of Wilds and Biggerstaff[8] with *p*-toluenesulfonic acid at 125–130° with a weight yield of only 35%. A total of 1.58 g. of active 3,4-dianisyl-3-hexene was obtained melting at 122.5–123.5° (literature,[6] 123–124°) with an activity of 5.02 mc./g.

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(4) N. H. Smith, K. E. Wilzbach, and W. G. Brown, *J. Am. Chem. Soc.*, **77**, 1033 (1955).

(5) E. M. Hodnett, C. F. Feldman, and J. J. Flynn, Jr., *Experientia*, **13**, 96 (1957).

(6) E. C. Dodds, L. Goldberg, W. Lawson, and R. Robinson, *Nature*, **141**, 247 (1938).

(7) E. C. Dodds, L. Goldberg, W. Lawson, and R. Robinson, *Proc. Roy. Soc. (London)*, **127B**, 140 (1939).

(8) A. L. Wilds and W. R. Biggerstaff, *J. Am. Chem. Soc.*, **67**, 789 (1945).

A New Indole Synthesis

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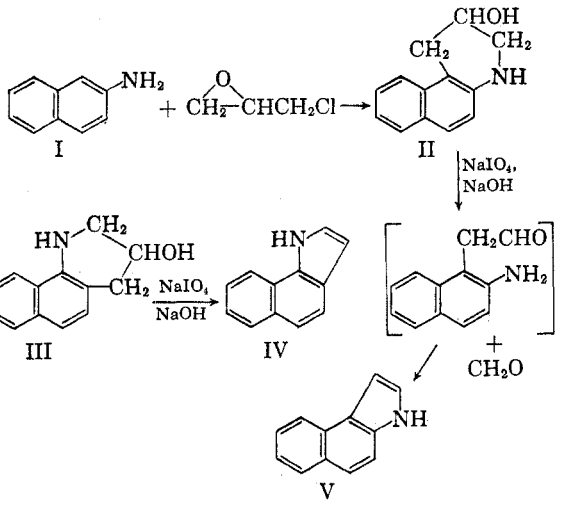
It is known that when hydroxyproline is oxidized with periodate, formaldehyde is split out and presumably an amino aldehyde is formed.[1] It would be expected that properly substituted β-hydroxypiperidines would likewise be oxidized, and the amino aldehydes thus formed might be cyclized to give indoles. Lange and others[2] have



reported the synthesis of suitable β-hydroxypiperidines, II and III, by the reaction of epichlorohydrin with β-naphthylamine and α-naphthylamine, respectively. The oxidation of II and III was investigated, therefore, and has led to the synthesis of 6,7-benzindole (IV) in 27% yield and the picrate of 4,5-benzindole (V) in 30% yield.

EXPERIMENTAL

Preparation of 4,5-benzindole (V) *by periodate oxidation of* II. II (2.00 g.) was dissolved in 50 ml. of ethanol and sodium metaperiodate (2.14 g.) was dissolved in 50 ml. of water. These solutions were added dropwise over a 3-hr. period to a 100-ml. solution of 8% sodium hydroxide through which steam was passing rapidly. The steam distillate was collected until the distillate no longer gave a red color with an acidic alcoholic solution of dimethylaminobenzaldehyde (Ehrlich's reagent). This required about 7 hr. The distillate was then extracted with benzene, the benzene extract dried over sodium sulfate, and the benzene removed *in vacuo*. The residual oil was dissolved in ethanol and treated with an ethanolic picric acid solution. Red needles of the picrate of V were recovered and dried; 1.20 g. (30%), dec. 205° with previous charring.

Anal. Calcd. for $C_{18}H_{12}N_4O_7$: C, 54.55; H, 3.05; N, 14.14. Found: C, 54.28; H, 3.20; N, 14.26.

An alkaline solution of the picrate was extracted with ether, and the ether extract was dried over potassium carbonate. The ether was removed, and the residual oil distilled, b.p. 145–150°/5 mm. The oil was purified further by dissolving it in benzene and chromatographing it on alumina. A sample boiling at 148°/5 mm. was analyzed.

Anal. Calcd. for $C_{12}H_9N$: C, 86.19; H, 5.43; N, 8.38. Found: C, 85.93; H, 5.45; N, 8.28.

An infrared spectrum of the oil (V) in chloroform showed a strong sharp band close to 2.9 μ but only weak absorption around 6.1 μ.

Preparation of 6,7-benzindole (IV) *by the oxidation of* III. Compound III (2.00 g.) was dissolved in 100 ml. of ethanol,

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