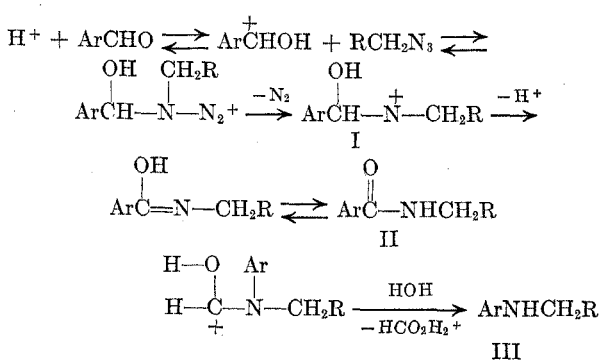
TABLE I

N-SUBSTITUTED ANILINES FROM BENZALDEHYDE AND AZIDES

Azide	Aniline Derivative	B.P. or M.P., °C	Refractive Index	Yield, %	Derivative	M.P. °C
n-Butyl	*N*-*n*-Butyl	120 (5 mm.)	n_D^{20} 1.5381	21.9	Hydrochloride	114–115
n-Hexyl	*N*-*n*-Hexyl	158 (28 mm.)[a]	n_D^{20} 1.4235[a]	25	*p*-toluenesulfonamide	67–68[a]
n-Octyl	*N*-*n*-Octyl	118 (25 mm.)[b]	n_D^{25} 1.6381	18	*p*-toluenesulfonamide	42–43[b]
Phenyl	*N*-Phenyl	53–54.5[c]		10	*p*-toluenesulfonamide	64[d]

[a] W. J. Hickinbottom, *J. Chem. Soc.*, 1119 (1937) reported b.p. 165° (35 mm.), n_D^{20} 1.4240, *p*-toluenesulfonamide, m.p. 69°. [b] W. J. Hickinbottom, *J. Chem. Soc.*, 1119 (1937), reported b.p. 119–120° (20 mm.), *p*-toluenesulfonamide, m.p. 41–42°. [c] P. P. Karpuklien, *J. Chem. Ind. (Moscow)*, **23**, 1627 (1929). [d] I. Goldberg, *Ber.*, **40**, 4543 (1907) reported m.p. 65°.

panied with tautomerization accounted for amide formation. The expected migration of an aryl group from carbon to nitrogen with subsequent formation of formanilides or their hydrolysis products, secondary amines (III), was not detected.



In the present work this migration is detected insofar as the predicted amines (III) are isolated. From each of three different primary alkyl azides and benzaldehyde the corresponding *N*-alkylaniline is isolated in 18–25% yields; diphenylamine is obtained from phenyl azide and benzaldehyde in 10% yield. Each reaction is carried out in benzene which contains equimolar quantities of azide and aldehyde together with sulfuric acid is catalyst.

Curiously amides (II) are not found. In contrast amides (II) (requiring no rearrangement) but not amines (III) were products of those reactions which used an excess of aldehyde as solvent in place of benzene.[2] Apparently aldehyde solvation of intermediates represses migration.

The presence of strong electron releasing groups in positions *ortho* or *para* to the carbonyl carbon atom inhibits a reaction between aldehydes and azides probably as a result of a decrease in the acidity of the corresponding aldehyde conjugate acids.[2] In the present work *p*-anisaldehyde is nearly quantitatively recovered from attempted reactions with alkyl azides in benzene or nitrobenzene containing sulfuric acid at temperatures ranging from 75–190°. On the other hand *p*-tolualdehyde was successfully transformed into *N*-*n*-butyl-*p*-toluidine using *n*-butyl azide.

Electron attracting ring substituents in the aromatic aldehyde had no apparent effect upon the efficiency of its transformation, using ethylene azidohydrin, into an oxazoline.[2] Unexpectedly *m*- and *p*-nitrobenzaldehyde have now been nearly quantitatively recovered from attempted reactions with *n*-butyl azide in benzene or nitrobenzene containing sulfuric acid at temperatures from 75–190°.

EXPERIMENTAL

Preparation of n-butylaniline. A mixture of 3.18 g. (0.03 mole) of benzaldehyde in 50 ml. of benzene and 5 ml. of concentrated sulfuric acid was warmed to 75°. At a rate which maintained gentle reflux, 2.97 g. (0.03 mole) of *n*-butyl azide was added dropwise with efficient stirring. Gas evolution was complete about 5 min. after the last drop of azide was added. The reaction mixture was then treated with 50 ml. of ice and water, the layers were separated, and the water layer was neutralized with sodium carbonate and extracted with ether. Distillation of the combined dried ether extracts gave 0.9 g. (21.9%) of *N*-*n*-butylaniline, b.p. 120° (2 mm.), n_D^{20} 1.5381, hydrochloride m.p. 114–115°.[3] Trace amounts of benzaldehyde were recovered from the benzene layer which also contained a large amount of tar.

In a similar manner *N*-substituted anilines were obtained from other azides and benzaldehyde; results are summarized in Table I.

In a similar reaction with 6.00 g. (0.05 mole) of *p*-tolualdehyde and 4.95 g. (0.05 mole) of *n*-butyl azide in benzene containing concentrated sulfuric acid there was obtained 1.6 g. (21%) of *p*-methyl-*N*-*n*-butylaniline, b.p. 105–106° (3 mm.)[4] hydrochloride, m.p. 150–151°,[4] picrate m.p. 90°.[4]

DEPARTMENT OF CHEMISTRY
TULANE UNIVERSITY
NEW ORLEANS, LA.

(3) J. Reilly and W. J. Hickinbottom, *J. Chem. Soc.*, **113**, 99 (1918).

(4) J. Reilly and W. J. Hickinbottom, *J. Chem. Soc.*, **117**, 103 (1920); **113**, 974 (1918).

Theophylline in the Mannich Reaction[1]

J. H. BURCKHALTER AND DALE R. DILL

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As a continuation of studies employing the Mannich reaction, we wished to determine if theo-

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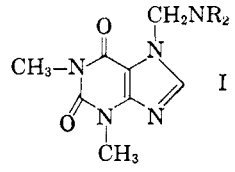
TABLE I

7-(SUBSTITUTED AMINOMETHYL)THEOPHYLLINES

No.	NR_2	M.P., °C (dec.)	Yield	Formula	Analyses, % C Calcd.	C Found	H Calcd.	H Found
1	Diethylamino	110	38	$C_{12}H_{19}N_5O_2$[a,b]	54.32	54.17	7.22	7.03
2	1-Pyrrolidinyl	108	61	$C_{12}H_{17}N_5O_2$[a,b]	54.74	54.47	6.51	6.50
3	1-Piperidinyl	111	87	$C_{13}H_{19}N_5O_2.1/2H_2O$	54.52	54.52	7.04	7.02
4	4-Morpholinyl	177	92	$C_{12}H_{17}N_5O_3$[c,d]	51.60	51.65	6.14	6.06
5	1-*N*-Methylpiperazinyl	131	83	$C_{14}H_{20}N_6.1/2H_2O$	51.82	51.60	7.03	7.14
6	7-Bis(1,4-piperazinedimethyl)	305	99	$C_{20}H_{26}N_{10}O_4.2H_2O$[e,f]	47.42	47.44	5.97	6.15

[a] Yield may be improved by obtaining second crop crystals. [b] Theophylline may be dissolved in the reaction mixture by mild heating on the steam bath, giving better yields. [c] Product precipitated from solution before unreacted starting material could be filtered from solution. [d] Could be recrystallized from absolute ethanol once before reverting to theophylline. [e] Piperazine hexahydrate was used. [f] Two moles each of theophylline and formalin were used to one mole of piperazine.

phylline, which has acidic properties, would undergo the reaction. Also, the products of the reaction, presumed to be 7-α-dialkylamino derivatives of caffeine (I),[2] would be of interest pharmacologically as stimulants, diuretics and hypotensives.



I

For the synthesis of type I compounds (Table I), a mixture of molecular equivalents of theophylline, secondary amine and aqueous formaldehyde was stirred at room temperature for a few minutes. In general, the water-soluble products separated from solution in excellent yield after refrigeration, but they could not be recrystallized without reverting to theophylline. Only in the case of the morpholinyl Mannich base was the product stable enough for one recrystallization.

7-Chloromethyltheophylline was made in 75% yield from chloromethylation of theophylline. It could not be recrystallized without decomposition. For example, when recrystallized from alcohol, it was converted quantitatively to the stable 7-hydroxymethyltheophylline. Treatment of the hydroxymethyl compound with thionyl chloride reconverted it to 7-chloromethyltheophylline.

An attempt was made to confirm the assignment of the position of the chloromethyl substituent in 7-chloromethyltheophylline by reducing it to caffeine. Since 1-chloromethylbenzotriazole has been reduced to 1-methylbenzotriazole,[5] chloromethyltheophylline was similarly treated with lithium aluminum hydride in tetrahydrofuran, but only a tar was obtained. Hydrogenation using palladium on charcoal gave only recovered starting material plus some 7-hydroxymethyltheophylline, the latter resulting from hydrolysis in the presence of the alcoholic solvent. Stannous chloride in hydrochloric acid also gave only starting material. However, further support for presumed substitution at position 7 may be suggested by the observation of the same infrared peaks for chloromethyl-, *N*-pyrrolidinyl-, and *N*-piperidylmethyltheophylline as were obtained with caffeine: 1370–1380 cm.$^{-1}$ (*N*-methyl) and 1015-1020 cm.$^{-1}$ (tertiary amine). The spectrum of theophylline does not exhibit these peaks.

Numerous attempts were made to prepare the Mannich bases of Table I by treating chloromethyltheophylline with two equivalents of the appropriate amine. In no case could the desired product be obtained, and theophylline was isolated as shown by analysis and melting point determination. Thus, it is strongly suggested that a Mannich base forms, as indicated by a vigorous reaction between the amine and chloromethyltheophylline, and attempts at purification result in decomposition, as do the products from the Mannich reaction. This conclusion is supported by the fact that the chloromethyl derivative does not decompose to theophylline upon recrystallization but to hydroxymethyltheophylline, which is a stable compound.[6]

Biological activity. Compounds 1 and 2 possessed no hypotensive action at 20 mg./kg. oral dosage in the perinephritic rat, while 1,2, and 4 exhibited

(2) Although two tautomeric structures may be written for theophylline, the fact that caffeine is obtained in good yield from the methylation of theophylline[3] suggests that alkylation at position 7 is highly favored over position 9. Other studies similarly suggest alkylation of theophylline at position 7.[4]

(3) J. M. Gulland and T. F. Macrae, *J. Chem. Soc.*, 662 (1933).

(4) J. M. Gulland, E. R. Holiday, and T. F. Macrae, *J. Chem. Soc.*, 1639 (1934); D. B. Ishay, *J. Chem. Soc.*, 3975 (1946).

(5) J. H. Burckhalter, V. C. Stephens, and L. A. R. Hall, *J. Am. Chem. Soc.* **74**, 3868 (1952).

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.

LABORATORY OF PHARMACEUTICAL CHEMISTRY
UNIVERSITY OF KANSAS
LAWRENCE, KAN.

(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

ERNEST M. HODNETT AND ROBERT GALLAGHER

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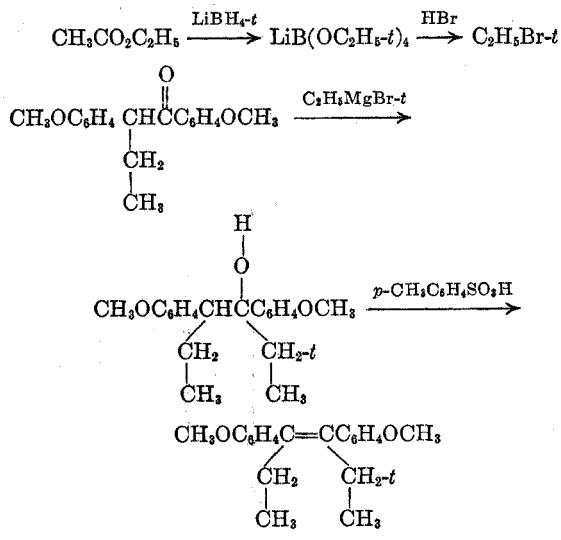
Radioactive 3,4-dianisyl-3-hexene (the dimethyl ether of stilbestrol) was needed recently for feeding experiments with poultry.[1] It was necessary to use tritium as the tagging isotope in spite of the more laborious assays anticipated because of the quantity of estrogen desired. Because the hormone 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).