under reduced pressure at 70°, at which temperature it decomposed to give the crude 3-fluoro compound. This crude material was dissolved in benzene, filtered, and chromatographed on alumina (Woelm, neutral, activity grade I). The product was eluted with 10% ether in benzene and recrystallized from methanol to give 0.24 g (24%) of III, mp 178–180°, $[\alpha]^{24}D$ +143°.

Anal. Calcd for $C_{18}H_{21}FO$: C, 79.38; H, 7.77; F, 6.98. Found: C, 79.39; H, 8.00; F, 6.83.

3-Fluoroestra-1,3,5(10)-trien-17β-ol (VI).—A solution of 1.00 g (3.69 mmoles) of 3-fluoroestra-1,3,5(10)-trien-17-one (III) in 100 ml of ethanol was treated with 4 ml of 10% NaOH solution and 0.53 g (14.0 mmoles) of $NaBH_4$. After 1 hr at room temperature the solution was poured into water, and the product was extracted with ether. The extract was washed with water, dried, and concentrated to dryness. The residue was recrystallized from hexane to yield 0.65 g (65%) of VI, mp 112–114°, $[\alpha]^{24}D$ +84°.

Anal. Calcd for $C_{18}H_{23}FO$: C, 78.80; H, 8.45; F, 6.92. Found: C, 79.00; H, 8.71; F, 6.67.

3-Fluoro-17α-methylestra-1,3,5(10)-trien-17β-ol (VII).—A solution of 0.84 g (3.09 mmoles) of 3-fluoroestra-1,3,5(10)-trien-17-one (III) in 80 ml of ether was treated with 3.5 ml of 3 *M* methylmagnesium bromide solution. The resulting mixture was stirred and refluxed for 1 hr, cooled, and treated with NH_4Cl solution. The ether layer was separated, washed with water, dried, and concentrated to dryness. The residue was recrystallized from ether–petroleum ether to give 0.40 g (45%) of VII, mp 108–110°, $[\alpha]^{24}D$ +58°.

Anal. Calcd for $C_{19}H_{25}FO$: C, 79.13; H, 8.74; F, 6.59. Found: C, 78.90; H, 8.75; F, 6.24.

Acknowledgment.—The authors wish to thank Mr. C. E. Childs and his staff of our Microanalytical Laboratory and Dr. J. M. Vandenbelt and his staff of our Physical Chemistry Laboratory for their valuable technical assistance. The authors are indebted to Dr. O. D. Bird, Dr. G. Rodney, and Dr. M. R. Callantine for the pharmacological activities presented in this paper.

Synthesis of Some Substituted Tryptophols of Possible Physiological Importance and a Study with 3-(2-Acetoxyethyl)-5-methoxyindole (5-Methoxytryptophol O-Acetate) on Sexual Maturation

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Received July 14, 1965

The unique psychopharmacological effects of ethanol, easily formed by biological processes, have been appreciated since antiquity. Recent studies have indicated that hydroxyl derivatives of histamine,[2a] the catecholamines,[2b,c] γ-aminobutyric acid,[3] tryptamine,[4] and serotonin[5] can be metabolites of these biogenic amines. Furthermore, the resultant biogenic alcohols may possess physiological properties. An example is γ-hydroxybutyric acid, a metabolite of γ-aminobutyric acid[3] which has effective sleep-producing properties.[6]

Tryptophol was identified as a metabolite of tryptamine in rats pretreated by the aldehyde dehydrogenase blocking agent, disulfiram.[4] Kveder, *et al.*,[5] presented good evidence that 5-hydroxytryptophol may be the second most important metabolite of serotonin in the rat, rather than N-acetylserotonin as first thought.[7] Bartholini, Pletscher, and Bruderer[8] found a neutral metabolite of serotonin released from isolated blood platelets by reserpine and have presented chromatographic evidence that it is 5-hydroxytryptophol. Evidence has also been presented for the presence of 5-methoxytryptophol and 5-hydroxytryptophol in pineal tissue[9] rather than β-carbolines, once thought to be constituents.[10]

It was necessary for us to prepare a collection of substituted tryptophols, the acetate esters, and related acids for our studies of metabolism, isolation, and pharmacology of these substances. Acetylation alters markedly the hormonal properties of 5-methoxytryptamine. The latter is without effect on frog-skin lightening while the acetylated analog (melatonin) is a potent frog-skin-lightening hormone[11,12] and displays marked inhibitory effects on the incidence of estrus in rats.[13] Therefore, it was of importance to see if chain acetylation of 5-methoxytryptophol might also produce a compound with special biological properties not seen in the precursor.

5-Methoxytryptophol was prepared by the lithium aluminum hydride reduction of either 5-methoxyindole-3-glyoxyloyl chloride or 5-methoxyindole-3-acetic acid. The reduction of the former produced a considerable amount of by-product which could not be removed by distillation or fractional crystallization. However, the 5-methoxytryptophol could be purified by conversion to a solid picrate derivative. Reduction of the acid gave a better product which was easily purified without recourse to the picrate. It was a yellow oil which was acetylated with acetic anhydride to give an oil that did not solidify, but that could be converted into a useful picrate. The metabolic fate and effects on sexual development of 3-(2-acetoxyethyl)-5-methoxyindole in the female rat were investigated; the latter study is reported in this paper, and the former will be reported elsewhere.

Other substituted tryptophols prepared were compounds which could be potential metabolites of 5-methoxytryptophol O-acetate and serve as chromatographic standards. For the selection of authentic compounds to be synthesized for chromatography, three possible metabolic transformations were anticipated. These are described together with synthetic routes (Chart I) being: (1) 6-hydroxylation only to give VII; (2) 6-hydroxylation and hydrolysis to give V; (3) 6-hydroxylation, ester hydrolysis, and oxidation to give III. Usually, indole-3-acetonitriles can

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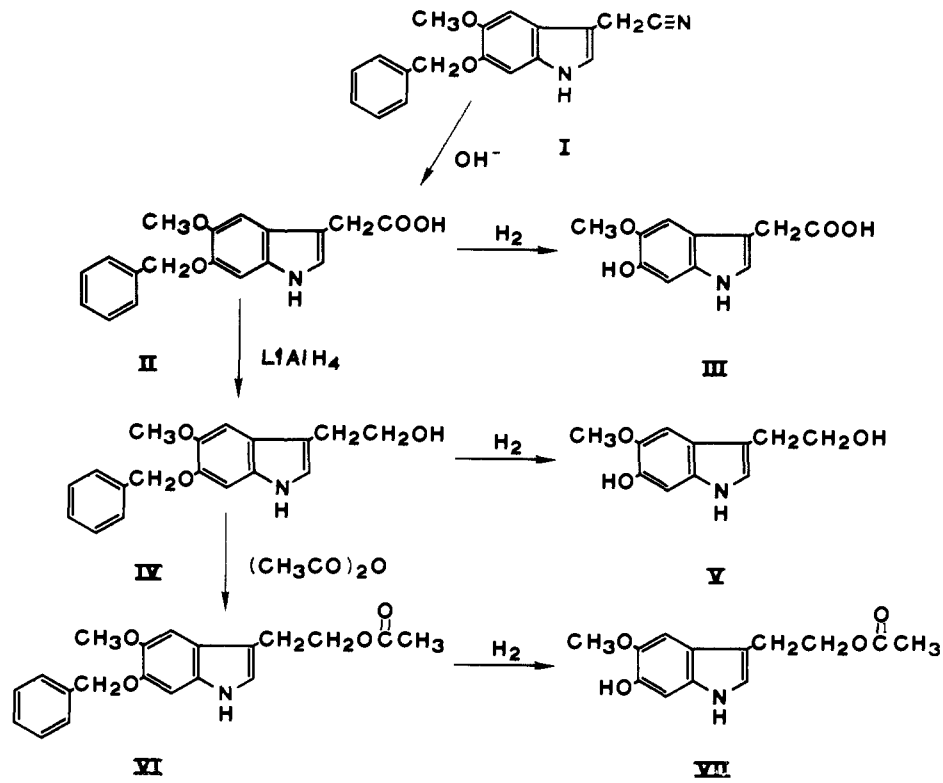
CHART I



be hydrolyzed to the acids with aqueous base. However, 6-benzyloxy-5-methoxyindole-3-acetonitrile (I) was resistant to this treatment, and saponification at higher temperature in refluxing propylene glycol was required. 5-Methoxytryptamine salts[14] were useful derivatives for some unstable 5,6-disubstituted indole acids prepared in this study. These derivatives and the picrates were useful for studies since they dissociated into the free compounds on chromatograms.

Effects of 3-(2-Acetoxyethyl)-5-methoxyindole (5-Methoxytryptophol O-Acetate) on Sexual Maturation of the Female Rat.—Pineal extracts,[15] melatonin,[13] and 5-methoxytryptophol[16] have been shown to inhibit partially, sexual development in maturing female rats. Since 5-methoxytryptophol O-acetate is chemically closely related both to melatonin and 5-methoxytryptophol, it was examined for its possible inhibitory effects.

Three groups of ten rats each were injected intraperitoneally, once daily, beginning at age 20 ± 3 days, with the test compounds. Animals of the first group (I) received 5-methoxytryptophol O-acetate picrate (50 μg), dissolved in 0.2 ml of propylene glycol; rats of the second group (II), picric acid (30 μg) in 0.2 ml of propylene glycol; and rats of the third group (III) received propylene glycol (0.2 ml) only. The rats were injected 6 of 7 days each week to the 90th day of life, at which time they were killed and the ovaries were excised and weighed. Vaginal smears were taken 6 of 7 days by medicine dropper beginning on the 60th day of life and the phases of estrus were established microscopically. The results of these studies are expressed in Table I.

TABLE I

EFFECTS OF 3-(2-ACETOXYETHYL)-5-METHOXYINDOLE (5-METHOXYTRYPTOPHOL O-ACETATE) ON THE SEXUAL DEVELOPMENT OF THE FEMALE RAT

Expt[a]	No. of[b] observations for estrus	Mean % of rats in estrus ± std dev	Mean ratio[c] of ovarian-body wt × 10⁴ ± std dev	Mean body wt (g) at 90 days
I-A	26	49.57 ± 6.38	4.99 ± 1.04	232
I-B	13	44.31 ± 3.59		
I-C	13	54.84 ± 3.42		
II-A	26	64.91 ± 2.37	5.22 ± 0.78	217
II-B	13	65.33 ± 3.03		
II-C	13	64.51 ± 1.98		
III-A	26	62.47 ± 2.04	5.21 ± 0.76	230
III-B	13	61.37 ± 2.24		
III-C	13	63.56 ± 1.02		

[a] In expt I, groups of ten rats were injected once daily (6 of 7 days each week) by the intraperitoneal route with 50 μg of 5-methoxytryptophol O-acetate picrate dissolved in 0.2 ml of propylene glycol. In expt II, a control of 30 μg of picric acid in 0.2 ml of propylene glycol was given. Experiment III was a control of 0.2 ml of propylene glycol given daily. Each experiment was divided into A, the sum of all 26 observations beginning at the 60th day of life, continuing to the 90th day; B, the first 13 observations to the 75th day of life; and C, in each case, the last 13 observations (75th to 90th day of life). [b] Each observation was made on a group of ten rats; thus, 26 group observations involved data based on 260 individual observations. [c] All animals were killed at 90 days; ovaries were removed and weighed.

The data clearly demonstrate a marked inhibitory effect on estrus. The fact that the standard deviation for I-A was considerably greater than for I-B and I-C suggests that expt I consisted of two sets of observations (*i.e.*, the agent exhibited a different potency in the first part of the experiment from that of the second).

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Therefore, the observations were divided so that data from the first thirteen observations could be compared with the last 13. The results from the control values (II and III) showed little difference between earlier (II-B and III-B) and later (II-C and III-C) observations; in expt I the difference of means between I-B and I-C was 10.53%. On taking the ratio of this to the standard deviation ±3.42 (t value), one finds that the quotient exceeds the critical value of t at the 1% probability level.

It appears that 5-methoxytryptophol O-acetate exerts a considerably greater inhibitory effect on estrus in immature than in mature animals. There was no significant decrease in ovarian-to-body weight ratios or of body weights of the estrus-inhibited group (Table I). It is concluded that 5-methoxytryptophol O-acetate has quantitatively similar inhibitory effects on rat estrus as melatonin and 5-methoxytryptophol. Recent studies of ours[17] demonstrated that 5-methoxytryptophol O-acetate is metabolized differently and more slowly than 5-methoxytryptophol. However, apparently the biochemical changes produced by acetylation do not result in greater inhibition of rat estrus.

Experimental Section

All indolic intermediates were purchased from the Regis Chemical Co., Chicago 10, Ill.

Reduction of 5-Methoxyindole-3-glyoxyloyl Chloride with Lithium Aluminum Hydride.—A solution of 2.35 g (1.0×10^{-2} mole) of 5-methoxyindole-3-glyoxyloyl chloride[18] in a small amount of dry tetrahydrofuran (THF) was added to 4.0 g (0.1 mole) of lithium aluminum hydride in 60 ml of THF, and the mixture was stirred magnetically overnight at room temperature. Excess hydride and the lithium aluminum complex were destroyed by water in THF. All solids were removed by suction filtration, and the filter cake was washed with ether. The clear filtrate was evaporated to dryness under vacuum. Distillation of the residue gave 1 g of a major fraction, bp 218–220° (5 mm). Silica gel thin layer chromatography of the fraction (10% methanol in $CHCl_3$) gave two spots of R_f 0.75 and 0.90. A number of variations of the reaction conditions were used in attempts to get a single product. None were successful. However, the picrate had a good melting point (115–116°, lit.[19] 117–118°) and produced a single-spot chromatogram.

Preparation of 5-Methoxytryptophol by Reduction of 5-Methoxyindole-3-acetic Acid.—5-Methoxyindole-3-acetic acid was prepared by the hydrolysis of 5-methoxyindole-3-acetonitrile which was prepared from the methosulfate of 5-methoxygramine.[20] A mixture of 0.2 g (5.3 mmoles) of lithium aluminum hydride and 0.5 g (2.4 mmoles) of 5-methoxyindole-3-acetic acid (mp 146–149°) in 115 ml of anhydrous ether was stirred at room temperature for 1 hr. Excess hydride was destroyed with 5–7 ml of water, and the reaction mixture was treated with 25 ml of 10% NaOH. The layers were separated, and the aqueous phase was extracted with three 15-ml portions of ether. The combined ether portion was dried, filtered, evaporated, and dried in a vacuum desiccator to yield 0.4 g (87%) of 5-methoxytryptophol as a viscous yellow oil. Thin layer chromatography with 1:10 methanol–$CHCl_3$ gave a discrete, Ehrlich-positive spot at R_f 0.67 with a trace of impurity indicated by a second faint spot. Attempted crystallization from ethyl acetate and n-hexane yielded an oil which was chromatographically pure, but did not solidify.

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.83; H, 6.92; N, 7.55.

A portion was converted to the picrate,[21] mp 116–116.5° (lit.[19] mp 117–118°).

3-(2-Acetoxyethyl)-5-methoxyindole Picrate.—A solution of 500 mg (2.62 mmoles) of 5-methoxytryptophol in 9 ml of acetic anhydride was heated for 5 hr at 90°. Solvent was removed *in vacuo* to yield 510 mg of 3-(2-acetoxyethyl)-5-methoxyindole as a tan oil. It was dissolved in a small amount of $CHCl_3$ and added to 500 mg of picric acid in 6.0 ml of $CHCl_3$. Partial evaporation and cooling yielded 821 mg (68%) of the desired picrate, mp 95–95.5°, unchanged on crystallization from $CHCl_3$.

Anal. Calcd for $C_{19}H_{18}N_4O_{10}$: C, 49.35; H, 3.92; N, 12.12. Found: C, 49.39; H, 4.07; N, 11.92.

6-Benzyloxy-5-methoxyindole-3-acetic Acid (II).—Powdered 6-benzyloxy-5-methoxyindole-3-acetonitrile[22] (3.10 g, 1.1×10^{-2} mole) 25.0 g of KOH, 100 ml of water, and 120 ml of propylene glycol were refluxed (stirring) for 18 hr. The mixture was cooled, diluted with water, treated with charcoal, and filtered. The filtrate was acidified to pH 3 and the solid product was extracted with $CHCl_3$. The combined extracts were reduced to 10 ml, cooled, and filtered to yield 1.33 g (40%) of air-dried product, mp 173–174°, after washing with n-hexane. A 1:1 $CHCl_3$–ether solution of 47 mg of the acid was treated with 30 mg of 5-methoxytryptamine to give a quantitative yield of the salt derivative,[14] mp 152–153°. One crystallization from toluene yielded an analytical sample, with melting point unchanged.

Anal. Calcd for $C_{29}H_{31}N_3O_5$: C, 69.46; H, 6.23; N, 8.38. Found: C, 69.59; H, 6.13; N, 8.17.

6-Hydroxy-5-methoxyindole-3-acetic Acid (III) **(5-Methoxytryptamine Salt).**—II (100 mg, 0.32 mmole) was hydrogenated in 25 ml of ethyl acetate over 25 mg of 10% palladium–charcoal in a Parr apparatus at 3 atm for 16 hr. Filtration and evaporation to dryness gave 70 mg (99%) of the crude acid, mp 125.5–128°. The acid was unstable in air, ethyl acetate solutions turning from yellow to green after a few minutes exposure. It was stabilized by conversion to the 5-methoxytryptamine salt, using ethyl acetate and ether as solvents. In this manner a 69% yield of tan crystals, mp 110° dec, were obtained. They turned dark green after several days in air at room temperature. One crystallization from a large volume of benzene yielded an analytical sample, mp 112° dec.

Anal. Calcd for $C_{22}H_{25}N_3O_5$: C, 64.22; H, 6.13; N, 10.21. Found: C, 64.07; H, 6.32; N, 9.96.

6-Benzyloxy-5-methoxytryptophol (IV).—A solution of 1.0 g (3.2 mmoles) of II in 150 ml of anhydrous ether was added to 500 mg of a stirred suspension of lithium aluminum hydride in 50 ml of ether to maintain gentle refluxing. The mixture was refluxed for 2 hr, the excess hydride was destroyed with water, and the product was extracted with ether. Drying ($MgSO_4$), filtration, and evpaoration of the ether yielded 643 mg (67%) of yellow crystals of IV, mp 121–123°. Two crystallizations from methanol yielded an analytical sample, mp 122–123°.

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.83; H, 6.45; N, 4.76.

6-Hydroxy-5-methoxytryptophol Picrate (V).—A solution of 100 mg (0.34 mmole) of IV in 25 ml of ethyl acetate was hydrogenated over 25 mg of 10% palladium–charcoal at 3 atm for 16 hr. Filtration and evaporation of the reaction mixture under vacuum yielded the product in the form of a tan oil. This was treated with 70 mg of picric acid in the minimum of boiling $CHCl_3$ to yield, on cooling, 45 mg (31%) of picrate, mp 135–136.5° dec. Two crystallizations from 5:1 $CHCl_3$–methanol gave an analytical sample, mp 138.5–139° dec.

Anal. Calcd for $C_{17}H_{16}N_4O_{10}$: C, 46.79; H, 3.70; N, 12.84. Found: C, 46.49; H, 3.98; N, 12.67.

3-(2-Acetoxyethyl)-6-benzyloxy-5-methoxyindole (VI).—A solution of 300 mg (1.0 mmole) of IV in 5 ml of acetic anhydride was heated with stirring at 90° for 5 hr. Evaporation of the solvent under vacuum left a tan oil. Crystallization from methanol gave 280 mg (82%) of white crystals, mp 87.5–88.5°. Recrystallization gave an analytical sample, mp 89–89.5°.

Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.64; H, 6.34; N, 4.04.

3-(2-Acetoxyethyl)-6-hydroxy-5-methoxyindole Picrate (VII).—A solution of 120 mg (0.35 mmole) of VI in 25 ml of ethyl acetate was hydrogenated (25 mg of 10% palladium–charcoal)

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at 3 atm for 16 hr. Filtration and evaporation of the filtrate to dryness under vacuum yielded a yellow oil. This was treated with 80 mg of picric acid in the minimum of boiling $CHCl_3$. On cooling and addition of a few drops of *n*-hexane, 155 mg (91%) of dark red crystals were obtained; mp 110–112° dec. Three crystallizations of the picrate from $CHCl_3$ containing a few drops of *n*-hexane gave pure VII, mp 114–114.5° dec.

Anal. Calcd for $C_{19}H_{18}N_4O_{11}$: C, 47.70; H, 3.79; N, 11.71. Found: C, 47.64; H, 3.99; N, 11.72.

Acknowledgment.—The authors wish to thank Mr. Jesse Green, Mr. Robert Wagar, Mrs. Kathleen Rice, and Mr. Martin Kampe for technical assistance.

Heterocyclic Amines. III. 3-Dimethylaminofuran[1]

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Received October 25, 1965

3-Dimethylaminofuran has been prepared from 3-furoyl azide by rearrangement to the urethan, methylation, and reduction, a route analogous to that recently reported for the synthesis of 3-dimethylaminothiophene.[3] The free base, isolated by preparative gas chromatography, was stable under vacuum or inert atmosphere, but it polymerized very rapidly in contact with the air. The amine readily reacted with methyl iodide to produce the quaternary salt, a white crystalline compound stable in air.

Pharmacology.[4]—3-Furyltrimethylammonium iodide, administered intravenously in a dose of 100 mg/kg, was fatal to two mice. The next lower dose, 31.6 mg/kg, was not lethal but produced ptosis, decreased activity, and irregular respiratory movements. A dose of 1 mg/kg administered quickly intravenously to a rat induced a biphasic vasomotor response of small magnitude; a similar response followed slow injection of 5 mg/kg. After this latter dose, epinephrine elicited a vasodepressor response, the pressor effect of norepinephrine was reduced, and the fall in blood pressure evoked by acetylcholine was markedly enhanced and prolonged.

For comparison, 3-thienyltrimethylammonium iodide[3] administered intravenously in doses of 100, 31.6, and 10 mg/kg to groups of two mice produced respectively 2, 1, and 0 fatalities. Ptosis, decreased locomotor activity, ataxia, and respiratory irregularities were observed in the survivors. In the rat, an intravenous dose of 0.5 mg/kg evoked a transient hypotensive response, and a dose of 5 mg/kg increased the magnitude and duration of the depressor response evoked by acetylcholine. In a cat, an intravenous dose of 1 mg/kg elicited a sharp, brief fall in blood pressure, but did not modify responses to epinephrine, norepinephrine, acetylcholine, or histamine. A dose of 4.7 mg/kg administered slowly intravenously to a cat caused complete respiratory arrest, a slight depressor response followed quickly by a marked rise in blood pressure, and copious salvation. Death ensued within a few minutes; marked fasciculations were evident for several minutes after death.

Phenyltrimethylammonium iodide was lethal to mice intravenously at doses of 10 mg/kg and higher. Increased locomotor activity and hypersensitivity to sound were observed at a dose of 1 mg/kg; ptosis and hyperpnea were noted after 3.16 mg/kg.

Experimental Section

3-Furoyl Azide.[5]—From 10.5 g (0.081 mole) of 3-furoyl chloride[6] in cold acetone and excess aqueous sodium azide, worked up as reported for the thiophene compound,[3] there was obtained 9.3 g (84%) of crude oily azide. Some crystallization occurred while evaporating the ether solution, but these crystals melted below room temperature.

Methyl N-(3-Furyl)carbamate.—Crude 3-furoyl azide (9.3 g, 0.068 mole) refluxed with 100 ml of absolute methanol for 12 hr; subsequent evaporation of the solvent gave 9.3 g of crude product, mp 76–83°. This crude material was satisfactory for methylation and the compound could be more readily purified at the next step. Recrystallization from ligroin gave 4.4 g (46%) of purified product, mp 81–83°, which upon vacuum sublimation gave white crystals: mp 82–83°; nmr spectrum[7] in $CDCl_3$, δ = 3.74 (s, CH_3, 3 H), 6.36 (q, 4-H of ring, 1 H), 7.24 (t, 5-H of ring, 1 H), 7.49 (broad s, NH,[8] 1 H), 7.74 (broad s, 2-H of ring, 1 H) ppm; J_{24} = 0.9 cps, J_{25} = 1.9 cps, J_{45} = 1.9 cps.

Anal.[9] Calcd for $C_6H_7NO_3$: C, 51.06; H, 5.00; N, 9.93; O, 34.01. Found: C, 51.02; H, 4.93; N, 9.92; O, 33.96.

Methyl N-Methyl-N-(3-furyl)carbamate.—Crude methyl N-(3-furyl)carbamate (14.1 g, 0.1 mole), 1 l. of anhydrous xylene, 32 ml (0.5 mole) of methyl iodide, and 45.8 g (1.0 mole) of a 52.5% dispersion of NaH in mineral oil were refluxed under nitrogen for 12 hr, with agitation by means of a Vibro Mixer.[10] The precipitated NaI and excess NaH were removed by filtration, and the xylene was evaporated under reduced pressure. The residue was chromatographed on 450 g of Merck alumina. The mineral oil from the NaH dispersion was removed by washing with petroleum ether. The methylated carbamate product was eluted with 4 l. of benzene. (Unmethylated starting material remained on the column and could be subsequently eluted with ether.) Evaporation of the benzene eluates gave an oil which distilled at 50–56° (0.2 mm) in a yield of 13.4 g (86%). An analytical sample was redistilled at 42° (0.06 mm): nmr spectrum in $CDCl_3$, δ = 3.26 (s, NCH_3, 3 H), 3.80 (s, OCH_3, 3 H), 6.60 (m, 4-H of ring, 1 H), 7.30 (t, 5-H of ring, 1 H), 7.55 (broad s, 2-H of ring, 1 H) ppm; J_{25} = 1.7 cps, J_{45} = 1.7 cps.

Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03; O, 30.94. Found: C, 54.34, 54.32; H, 5.93, 5.77; N, 9.10, 9.12; O, 30.81, 31.02.

3-Dimethylaminofuran.—Methyl N-methyl-N-(3-furyl)carbamate (5 g, 0.032 mole), dissolved in 50 ml of anhydrous tetrahydrofuran was added to a solution of 2.4 g (0.064 mole) of $LiAlH_4$ in 100 ml of anhydrous tetrahydrofuran. The mixture was refluxed under dry nitrogen for 70 hr, cooled to room temperature, 5 ml of water was added with vigorous stirring, followed by the addition of 2 mg of hydroquinone. The solid was removed by

(1) (a) This work has been supported in part by U. S. Public Health Service Research Grant No. GM 10264. (b) Presented before the Division of Medicinal Chemistry at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Aug 1964. (c) Previous paper: J. B. Sullivan and W. C. McCarthy, *J. Heterocyclic Chem.*, **2**, 103 (1965).

(2) Fellow of the American Foundation for Pharmaceutical Education and Josiah Kirby Lilly Memorial Fellow for 1962–1964.

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(6) (a) H. Gilman and R. R. Burtner, *ibid.*, **55**, 2903 (1933). (b) The 3-furoic acid was prepared according to S. Gronowitz and G. Sorlin, *Arkiv Kemi*, **19**, 515 (1962).

(7) Nmr spectra were taken at 60 Mc and reported as δ values in ppm from tetramethylsilane (internal reference). Coupling constants are reported in cps ±0.2.

(8) Identified by deuteration in heavy water plus deuteriomethanol.

(9) Elemental analyses by A. Bernhardt, Mülheim (Ruhr), Germany.

(10) In similar runs with conventional stirring, yields of only about 20% were obtained, apparently because the sodium salt of the urethan formed a coating on the NaH particles.