[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF WASHINGTON]

Furyl- and Tetrahydrofuryl-alkylamines

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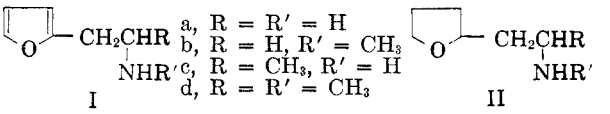
A series of β-(2-furyl)alkylamines has been prepared from furfural, and the corresponding tetrahydrofuryl compounds have been obtained by catalytic hydrogenation in the presence of palladium catalyst. These substances are structurally related to the sympathomimetic drugs.

The furyl- and tetrahydrofuryl-alkylamines have been given only cursory study as sympathomimetic agents in the past, apparently because the few members of the series that had been tested showed low pressor activity. In order to obtain more information relating chemical structure to pharmacological activity, several new members of this series have been synthesized. Pharmacological evaluation of these compounds for several sympathomimetic responses is being performed in the laboratories of the College of Pharmacy of the University of Wyoming, and will be reported elsewhere.

β-(2-Furyl)ethylamine (Ia) was first prepared by Windaus and Dalmer[3] from β-(2-furyl)propionic acid by a Curtius degradation. They reported that the amine was a vasodepressor in cats, and that it contracted the isolated uterine muscle of guinea pigs. The same amine has been prepared by reduction of 2-furylacetaldoxime[4,5] with sodium amalgam, and by electrolytic reduction[6] of ω-nitro-2-vinylfuran. β-(2-Furyl)isopropylamine (Ic) has been previously prepared from the oxime of 2-furylacetone by reduction with sodium[7] and by hydrogenation[8] in the presence of Raney nickel catalyst. It is reported to be one third as active as amphetamine as a pressor agent in dogs.[9]

This paper reports the preparation of the above two amines by the very convenient reduction of the corresponding nitroalkenes with lithium aluminum hydride. These primary amines were converted to the analogous N-methyl secondary amines (Ib and d) by the method of Blicke and Lu,[10] which involves reaction with chloral to form the N-formyl derivative, followed by reduction with lithium aluminum hydride.



β-(Tetrahydro-2-furyl)ethylamine (IIa) has been previously prepared from β-(2-furyl)propionic acid by hydrogenation of the ring with palladium on charcoal as the catalyst, followed by a Curtius degradation.[3] It was reported to have no effect on blood pressure, but to be twice as active as the furyl compound in regard to contraction of the isolated guinea pig uterus. Takamoto[6] attempted to prepare this amine from the corresponding furan (Ia) by hydrogenation with platinum catalyst, but cleavage of the ring occurred. As reported in this paper, palladium performs satisfactorily as a catalyst for this reduction.

EXPERIMENTAL[11-13]

ω-Nitro-2-vinylfuran. This compound was prepared by a modification of the method reported by Worrall[14] for ω-nitrostyrene. A black material was obtained, from which the desired product could not be separated by crystallization, but steam-distillation was satisfactory for this initial purification. On a three-mole run, there was obtained, after steam-distillation and recrystallization from dilute alcohol, a yield of 61%, m.p. 75–76°. Thiel and Landers[15] reported m.p. 74–75°.

β-(2-Furyl)ethylamine. From 139 g. (1 mole) of ω-nitro-2-vinylfuran and 76 g. (2 moles) of lithium aluminum hydride in ether solution, there was obtained 68.3 g. (62%) of amine collected from 60–70° (20 mm.).

β-(Tetrahydro-2-furyl)ethylamine. A mixture of 15 g. (0.134 mole) of β-(2-furyl)ethylamine, 13 ml. (0.156 mole) of concentrated hydrochloric acid, 100 ml. of absolute ethanol, and 0.5 g. of palladium catalyst[16] was shaken under 90 p.s.i. of hydrogen for six hours. Absorption stopped after 2½ hours, at which time the theoretical amount of hydrogen

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(2) Abstracted from the Ph.D. thesis of R. J. Kahl, May 1955.

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(9) Alles and Feigen, *J. Pharmacol. Exptl. Therap.*, **72**, 265 (1941).

(10) Blicke and Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952).

(11) Melting points are uncorrected.

(12) Part of the experimental work reported here has been done in the laboratories of the College of Pharmacy, University of Wyoming.

(13) Cost of chemical analyses has been paid by a grant from the Medical and Biological Research Fund of the State of Washington.

(14) Worrall, *Org. Syntheses*, **Coll. Vol. 1**, 405 (1932).

(15) Thiel and Landers, *Ann.*, **369**, 300 (1909).

(16) Starr and Hixon, *Org. Syntheses*, **Coll. Vol. 2**, 566 (1943).

had been absorbed. The catalyst was filtered and the alcohol was distilled off. The residue was dissolved in dilute hydrochloric acid and extracted with ether. The aqueous layer, cooled in an ice-bath, was made alkaline with sodium hydroxide solution and extracted with ether. From this ether extract there was obtained a yield of 7.1 g. (47%) of product that distilled at 70–75° (20 mm.), n_D^{21} 1.4565.

N-Formyl-β-(2-furyl)ethylamine. Reaction of 24.3 g. (0.22 mole) of β-(2-furyl)ethylamine with 32.5 g. (0.22 mole) of chloral[10] gave 20 g. (59%) of product collected at 125–135° (2 mm.). A sample was further purified for analysis, b.p. 129–130° (2 mm.), n_D^{27} 1.5056.

Anal. Calc'd for $C_7H_9NO_2$: N, 10.06. Found: N, 9.80.

N-Methyl-β-(2-furyl)ethylamine. Reduction of 20 g. (0.143 mole) of N-formyl-β-(2-furyl)ethylamine with 9.9 g. (0.26 mole) of lithium aluminum hydride[10] in ether, after working up in the usual manner, produced 14 g. (78%) of amine which boiled from 66 to 74° (20 mm.). Upon redistillation, the compound boiled at 69–70° (20 mm.), n_D^{26} 1.4720.

Anal. Calc'd for $C_7H_{11}NO$: N, 11.19. Found: N, 11.00.

The *phenylthiourea derivative* was recrystallized from dilute alcohol, m.p. 68.5–69.5°.

Anal. Calc'd for $C_{14}H_{16}N_2OS$: N, 10.76. Found: N, 10.80.

N-Methyl-β-(tetrahydro-2-furyl)ethylamine. The theoretical amount of hydrogen was taken up in 2 hours by a mixture of 14 g. (0.112 mole) of N-methyl-β-(2-furyl)ethylamine, 12 ml. of concentrated hydrochloric acid, 100 ml. of absolute ethanol, and 0.5 g. of palladium catalyst[16] shaken under an initial hydrogen pressure of 91 p.s.i. A yield of 6.9 g. (48%) of the amine was collected at 76–82° (20 mm.). The analytical sample distilled at 78–79° (20 mm.), n_D^{21} 1.4536.

Anal. Calc'd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.17; H, 11.72; N, 10.70.

The *phenylthiourea derivative* was recrystallized from dilute alcohol, m.p. 62–63°.

Anal. Calc'd for $C_{14}H_{20}N_2OS$: C, 63.60; H, 7.63; N, 10.60. Found: C, 63.19; H, 7.28; N, 10.90.

1-(2-Furyl)-2-nitro-1-propene. A mixture of 480 g. (5 moles) of furfural, 375 g. (5 moles) of nitroethane, 895 ml. of absolute alcohol, and 100 ml. of *n*-butylamine was allowed to stand in the dark at room temperature for five days. The mixture was cooled and the yellow crystals were filtered. After recrystallization from alcohol, a yield of 543 g. (71%), m.p. 50–51°, was obtained. Hass, *et al.*,[8] reported m.p. 48–49°.

β-(2-Furyl)isopropylamine. From 153 g. (1 mole) of 1-(2-furyl)-2-nitro-1-propane and 76 g. (2 moles) of lithium aluminum hydride in ether solution, there was obtained 80 g. (64%) of amine collected from 68–75° (20 mm.).

β-(Tetrahydro-2-furyl)isopropylamine. The theoretical amount of hydrogen was taken up in 2½ hours by a mixture of 15 g. (0.12 mole) of β-(2-furyl)isopropylamine, 12.5 ml. of concentrated hydrochloric acid, 100 ml. of absolute alcohol, and 0.4 g. of palladium catalyst[16] shaken under an initial hydrogen pressure of 94 p.s.i. A yield of 6.4 g. (41%) was collected at 78–82° (20 mm.). The analytical sample boiled at 80–81° (20 mm.), n_D^{22} 1.4570.

Anal. Calc'd for $C_7H_{15}NO$: N, 10.84. Found: N, 11.00.

The *phenylthiourea derivative* was recrystallized from dilute alcohol, m.p. 116–117°.

Anal. Calc'd for $C_{14}H_{20}N_2OS$: C, 63.61; H, 7.61; N, 10.60. Found: C, 63.84; H, 7.36; N, 10.40.

N-Formyl-β-(2-furyl)isopropylamine. Reaction of 17.1 g. (0.137 mole) of β-(2-furyl)isopropylamine with 20 g. (0.137 mole) of chloral[10] gave 18.5 g. (89%) of the amide collected at 125–130° (2 mm.). A sample was further purified for analysis, b.p. 126–127° (2 mm.), n_D^{26} 1.4960.

Anal. Calc'd for $C_8H_{11}NO_2$: N, 9.15. Found: N, 8.95.

N-Methyl-β-(2-furyl)isopropylamine. Reduction of 18.5 g. (0.122 mole) of N-formyl-β-(2-furyl)isopropylamine with 9.9 g. (0.26 mole) of lithium aluminum hydride in ether gave 14 g. (84%) of the amine that boiled from 78 to 88° (30 mm.). The analytical sample distilled at 85–86° (30 mm.), n_D^{27} 1.4655.

Anal. Calc'd for $C_8H_{13}NO$: N, 10.06. Found: N, 10.00.

The *phenylthiourea derivative* was recrystallized from ethanol, m.p. 103.5–104.5°.

Anal. Calc'd for $C_{15}H_{18}N_2OS$: N, 10.20. Found: N, 10.00.

N-Methyl-β-(tetrahydro-2-furyl)isopropylamine. The theoretical amount of hydrogen was absorbed in 2½ hours by a mixture of 14 g. of N-methyl-β-(2-furyl)isopropylamine, 12 ml. of concentrated hydrochloric acid, 100 ml. of absolute ethanol, and 0.4 g. of palladium catalyst[16] shaken under an initial hydrogen pressure of 92 p.s.i. A yield of 6.3 g. (43%) was collected in the fraction that boiled at 86 to 91° (20 mm.). Upon redistillation, the compound boiled at 87–88° (20 mm.), n_D^{21} 1.4533.

Anal. Calc'd for $C_8H_{17}NO$: C, 67.08; H, 11.97; N, 9.78. Found: C, 66.76; H, 11.69; N, 10.10.

The *phenylthiourea derivative* was recrystallized from ethyl alcohol, m.p. 112–113°.

Anal. Calc'd for $C_{15}H_{22}N_2OS$: C, 64.70; H, 7.97; N, 10.06. Found: C, 64.92; H, 7.87; N, 9.90.

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