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Substituted Tetrahydrofurans. 4-Oxo-2,2,5,5-tetraalkyltetrahydro-3-furonitriles, -3-Furamides, and -3-Thiofuramides

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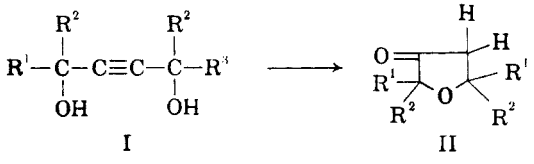
Bromination of 2,2,5,5-tetraalkyltetrahydro-3-furanones gave the bromotetrahydro-3-furanones (III). Treatment of III with alcoholic potassium cyanide solution yielded the corresponding tetrahydro-3-furonitriles (IV). IV underwent alkali peroxide-catalyzed hydrolysis to the amides, V, and added the elements of hydrogen sulfide with the formation of thioamides (VI). Bromination of IVa gave the α-bromonitrile, VIIa, which decomposed (probably with fragmentation of the furanone ring) during attempted metatheses with sodium alkoxides and alkali-peroxide catalyzed hydrolysis. Bromination of Va gave the corresponding α-bromoamide (VIIIa) which when treated with sodium ethoxide yielded the α-ethoxy-substituted amide (IX). The bromotetrahydro-3-furanone, IIIa, fails to partake in nucleophilic displacement reactions with reagents of varying degrees of basic strength. Several of the compounds described herein were found to possess a magnitude of hypnotic activity which prompted intensive biological study.

Recent developments in the technology of acetylene have made possible the bulk manufacture of a variety of acetylenic glycols (I) which can be cyclized[2] readily to form substituted tetrahydro-3-furanones (II). A search of the literature uncovered no references to the pharmacological evaluation of II or of any of its derivatives. A study was therefore undertaken of a number of

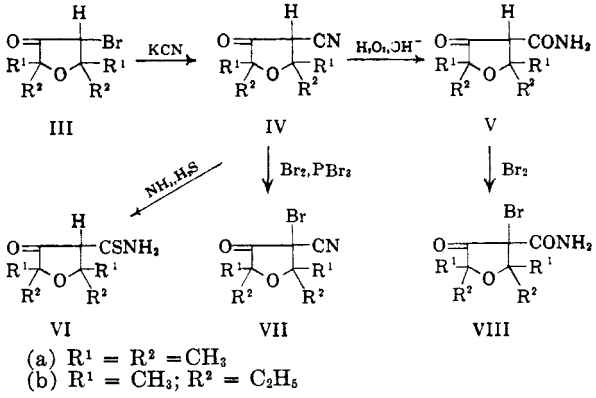


I II

reactions which II was expected to undergo, with the ultimate objective of preparing a variety of tetrahydrofuran derivatives substituted with "pharmacodynamogenic" groupings. In this communication the synthesis and range of hypnotic activity of a variety of 4-oxotetrahydro-2,2,5,5-tetraalkyl-3-furamides and 3-thiofuramides are reported.

Bromination of II gave 4-bromodihydro-2,2,5,5-tetraalkyl-3-(2H)-furanone (III) which was converted to the corresponding nitrile (IV) when stirred and refluxed with potassium cyanide in alcoholic solution. Alkali peroxide hydrolysis of the nitrile (IVa) gave the crystalline amide, 4-oxotetrahydro-2,2,5,5-tetramethyl-3-furamide (Va). The homologous nitrile (IVb), however, gave syrupy products which showed no tendency to crystallize even after months of refrigeration. Both nitriles, IV, when treated under pressure with a mixture of ammonia and hydrogen sulfide, were smoothly converted to thioamides (VI).

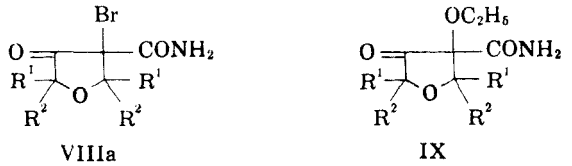
The nitrile, IVa brominated slowly in the presence of catalytic amounts of phosphorus tribro-



III IV V VI VII VIII

(a) $R^1 = R^2 = CH_3$
(b) $R^1 = CH_3$; $R^2 = C_2H_5$

mide to yield the bromonitrile (VIIa). All attempts to convert VIIa to the corresponding ethoxy-substituted nitrile by treatment with the equivalent quantity of sodium ethoxide or to the corresponding bromoamide (VIIIa) by alkali-peroxide catalyzed hydrolysis resulted, probably, in fragmentation of the furanone ring. The preparation was attempted therefore, of 3-bromo-4-oxotetrahydro-2,2,5,5-tetramethyl-3-furamide (VIIIa) by bromination of the amide, Va. A product was obtained which was assigned the structure VIIIa on the basis of the following observations: (1). It is devoid of a halogen-like odor, (2). It forms neutral solutions which do not liberate iodine from an acidulated potassium iodide-potassium iodate solution, and (3). It undergoes normal displacement with ethoxide to yield 3-ethoxy-4-oxo-2,2,5,5-tetramethyl-3-furamide (IX).



VIIIa IX

Richet, Dulou, and Dupont[3] previously described the abnormal behavior of the bromoketone,

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(2a) G. Dupont, *Compt. rend.*, **152**, 1486 (1911); (2b) G. Dupont, *Compt. rend.*, **153**, 275 (1911) [*Chem. Abstr.*, **5**, 3408 (1911)].

(3) H. Richet, R. Dulou, and G. Dupont, *Bull. soc. chim.*, 693 (1947).

IIIa, when hydrolyzed and also noted that attempted displacement of bromine in IIIa with acetate yielded none of the desired acetoxy derivative. On the other hand Richet and co-workers reported the facile conversion of IIIa to the corresponding nitrile (IVa), a reaction which was employed in the present study. It was observed additionally in these laboratories that IIIa fails to undergo displacement with diethylamine, thiourea, potassium thiocyanate, and potassium sulfhydrate.

All of the compounds described herein were evaluated in the Pharmacological Section of these laboratories. Hypnotic activity and toxicity data on several of the substances discussed above are summarized in Table I.

TABLE I

HYPNOTIC ACTIVITY AND ACUTE ORAL TOXICITY OF SEVERAL 2,2,5,5-TETRAALKYLTETRAHYDRO-3-FURANONE DERIVATIVES

Compound	Mouse HD_{50} mg./Kg. oral	Mouse LD_{50} mg./Kg. oral
IVa	500	700–900
Va	1000–1250	2000–3000
VIa	630	1300
VIb	500	600
VIIIa	1750	3000
IX	>2000	

It is clear from an inspection of the activity-toxicity data that the amide Va and thioamide VIa possess the most favorable activity-toxicity relationship. Substitution of Va with a bromine atom or ethoxy group on carbon 3 is accompanied by a decrease in both activity and toxicity (VIIIa, IX). The replacement of two methyl groups in VIa by ethyl groups (VIb) increased activity slightly but caused a marked increase in toxicity. Compounds Va and VIa were selected for intensive biological study, the results of which will be submitted for publication elsewhere.

Acknowledgment. We are indebted to Drs. R. J. Schachter and E. Kimura for the preliminary screening data and to Drs. George W. Mast and Kurt Ladenburg for their active support and encouragement of this investigation.

EXPERIMENTAL[4]

The descriptions in the literature of the methods employed for the preparation of the known tetrahydro-2,2,5,5-tetraalkyl-3-furanones, 4-bromotetrahydro-2,2,5,5-tetramethyl-3-furanone, and 4-oxotetrahydro-2,2,5,5-tetramethyl-3-furonitrile are very brief. The methods which were employed in this investigation for the synthesis of these substances are therefore described below.

Tetrahydro-2,2,5,5-tetraalkyl-3-furanones. A solution of 200 g. of 2,5-dimethyl-3-hexyne-2,5-diol in 500 ml. of water was rapidly steam-distilled in the presence of 40 g. of mercuric sulfate. The distillate was saturated with potassium carbonate, and the oily layer was separated, dried over potassium carbonate, and fractionated. Tetrahydro-2,2,5,5-tetramethyl-3-furanone distilled at 150–151°; yield, 150 g., n_D^{20} 1.4211. Literature constants:[2a] b.p., 149°; n_D 1.4198.

Tetrahydro-2,5-diethyl-2,5-dimethyl-3-furanone was similarly prepared by steam-distillation of a mixture of 300 g. 3,6-dimethyl-4-octyne-3,6-diol, 1450 ml. of water, and 60 g. of mercuric sulfate; yield: 210 g. (70%); b.p. 192–195°; n_D^{25} 1.4349. Literature constants:[2b] b.p.: 192°; n_D 1.4368.

4-Bromo-2,2,5,5-tetraalkyltetrahydro-3-furanones. One mole (142.2 g.) of tetrahydro-2,2,5,5-tetramethyl-3-furanone was dissolved in 300 ml. of carbon tetrachloride. This solution was stirred and treated dropwise during the course of about ¾ of an hour at a temperature of 3–5° with 160 g. (1 mole) of bromine.[5] After completion of the addition of bromine, hydrogen bromide was expelled from the reaction mixture by a stream of nitrogen. Enough aqueous 5% sodium bicarbonate (about 250 ml.) was added to make the reaction mixture slightly basic. The organic layer was separated, dried over potassium carbonate, and fractionated. 4-Bromotetrahydro-2,2,5,5-tetramethyl-3-furanone distilled at 87–89°/15 mm. and showed n_D^{10} 1.4719; yield: 194 g. (88%). Richet[6] reported b.p. 106°/25 mm. and n_D^{10} 1.4730.

4-Bromo-2,5-diethyl-2,5-dimethyltetrahydro-3-furanone was prepared in the same way in 75% yield. It distilled at 127–130°/25 mm. and had n_D^{25} 1.4725. A sample prepared for analysis distilled at 78°/2 mm. and showed n_D^{25} 1.4714.

Anal. Calc'd for $C_{10}H_{17}BrO_2$: C, 48.21; H, 6.88. Found: C, 48.42; H, 6.79.

4-Oxo-2,2,5,5-tetraalkyltetrahydro-3-furonitriles. A mixture of 221 g. (1 mole) of 4-bromotetrahydro-2,2,5,5-tetramethyl-3-furanone, 71.6 g. (1.1 moles) of potassium cyanide, and 400 ml. of isopropyl alcohol was stirred and refluxed for 20 hours. The hot mixture was cooled, filtered, and fractionated. 4-Oxotetrahydro-2,2,5,5-tetramethyl-3-furonitrile distilled at 87–89°/15 mm.; yield: 160 g. (96%); n_D^{25} 1.4379. Richet, Dulou, and Dupont[3] reported b.p. 90°/18 mm.

When a mixture of 124.5 g. (0.5 mole) of 4-bromo-2,5-diethyl-2,5-dimethyltetrahydro-3-furanone, 35.8 g. (0.55 mole) of potassium cyanide, and 300 ml. of 95% ethanol was refluxed and stirred for 20 hours, 2,5-diethyl-2,5-dimethyl-4-oxotetrahydro-3-furonitrile was obtained upon workup; yield 84.1 g. (86.5%); b.p. 75°/2 mm., n_D^{25} 1.4444. Redistillation of a sample for analysis produced no change in boiling point or refractive index.

Anal. Calc'd for $C_{11}H_{17}NO_2$: C, 67.69; H, 8.78; N, 7.18. Found: C, 67.78; H, 8.59; N, 6.81.

4-Oxo-2,2,5,5-tetraalkyltetrahydro-3-furamides. A mixture of 24 g. (0.15 mole) of 4-oxotetrahydro-2,2,5,5-tetramethyl-3-furonitrile, 60 ml. of 30% hydrogen peroxide, and 80 ml. of isopropyl alcohol was cautiously treated with 6 ml. of 6 *N* sodium hydroxide during a period of 10 minutes. The reaction mixture was maintained at 40–45° with external cooling for 1 hour, heated at 50° for 3 hours, neutralized with 5% sulfuric acid, and steam-distilled. Steam-distillation was stopped after about 300 ml. of distillate had been collected. 4-Oxotetrahydro-2,2,5,5-tetramethyl-3-furamide crystallized on cooling from the residual solution in the distillation flask; yield 15.5 g.; m.p. 137–139°. Recrystallization of the amide from water did not change the melting point.

Anal. Calc'd for $C_9H_{15}NO_3$: C, 58.30; H, 8.16; N, 7.50. Found: C, 58.37; H, 8.37; N, 7.47.

(4) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. All melting and boiling points are uncorrected.

(5) Instant decolorization usually occurs with the evolution of hydrogen bromide. If decolorization does not occur after about 10% of the required amount of bromine has been added, addition of bromine should be stopped and the reaction initiated by irradiation with ultraviolet light. Sometimes the reaction starts spontaneously after several hours.

(6) H. Richet, *Ann. chim.*, [12], **3**, 317 (1948).

When hydrolysis of 4-oxo-2,5-diethyl-2,5-dimethyltetrahydro-3-furonitrile was attempted by the method described above a heavy syrup was obtained which failed to crystallize after months of storage in a refrigerator.

4-Oxo-2,2,5,5-tetraalkyltetrahydro-3-thiofuramides. 4-Oxotetrahydro-2,2,5,5-tetramethyl-3-furonitrile (20.9 g., 0.125 mole) was dissolved in 40 ml. of half-saturated alcoholic ammonia solution. The resulting solution was saturated with hydrogen sulfide, stoppered tightly, and set aside for 18 hours at room temperature. The yellow crystalline product was removed by filtration, and washed with a small amount of alcohol; yield: 9.8 g., m.p. 140–141°. Recrystallization elevated the melting point to 141–142° and gave material which analyzed correctly for 4-oxotetrahydro-2,2,5,5-tetramethyl-3-thiofuramide.

Anal. Calc'd for $C_9H_{15}NO_2S$: C, 53.70; H, 7.51; N, 6.96. Found: C, 54.12; H, 7.26; N, 7.05.

4-Oxo-2,5-diethyl-2,5-dimethyltetrahydro-3-thiofuramide was similarly prepared although in lower yield from 19.5 g. (0.1 mole) of the corresponding nitrile. Filtration of the reaction mixture yielded 1.5 g. of a white crystalline product which was devoid of sulfur. The filtrate was concentrated *in vacuo* and the residue was extracted with petroleum ether. Chilling of the petroleum ether solution gave 4.5 g. of crude 4-oxo-2,5-diethyl-2,5-dimethyltetrahydro-3-thiofuramide, m.p. 130–135°. Two recrystallizations from a 4:1 petroleum ether-benzene mixture gave material which melted at 134–135°

Anal. Calc'd for $C_{11}H_{19}NO_2S$: C, 57.61; H, 8.35. Found: C, 57.88; H, 8.27.

3-Bromo-4-oxotetrahydro-2,2,5,5-tetramethyl-3-furonitrile. A mixture of 153 g. (1.0 mole) of 4-oxotetrahydro-2,2,5,5-tetramethyl-3-furonitrile and 144 g. (0.9 mole) of bromine was cooled in an ice-bath and treated with 4.5 ml. of phosphorus tribromide.[7] Addition of phosphorus tribromide was accompanied by the evolution of heat. When the mixture was no longer exothermic it was heated at 80° for 32 hours and let cool overnight. The crystalline product was separated by filtration and washed with a little benzene; m.p. 115–120°. Recrystallization from benzene gave material which melted at 121–122°. Yield after recrystallization 31 g.

Anal. Calc'd for $C_9H_{12}BrNO_2$: C, 43.90; H, 4.89; N, 5.64. Found: C, 43.56; H, 5.61; N, 5.55.

All attempts to metathesize this nitrile with sodium methoxide or sodium ethoxide to form the corresponding 3-alkoxy-substituted nitriles resulted in probable fragmentation of the furanone ring. This was concluded on the basis of the isolation of water-soluble materials of high oxygen content.

When the nitrile was subjected to alkali-peroxide catalyzed hydrolysis, decomposition of the furanone ring also appears to have been the principle reaction pathway. Water-soluble acidic substances of high oxygen content were the only products which could be isolated.

3-Bromo-4-oxotetrahydro-2,2,5,5-tetramethyl-3-furamide. A mixture of 37 g. (0.20 mole) of 4-oxotetrahydro-2,2,5,5-tetramethyl-3-furamide, 250 ml. of chloroform, and 32 g. (0.175 mole) of bromine was stirred and refluxed for 22 hours and cooled. The yellow crystalline product, m.p. 190–192°, was separated and recrystallized from benzene; m.p. 195–197° and yield 13.5 g. after recrystallization.

Anal. Calc'd for $C_9H_{14}BrNO_3$: N, 5.30. Found: N, 5.30.

3-Ethoxy-4-oxotetrahydro-2,2,5,5-tetramethyl-3-furamide. 3-Bromo-4-oxotetrahydro-2,2,5,5-tetramethyl-3-furamide (6.7 g., 0.025 mole) dissolved in 100 ml. of ethanol was added to a solution of sodium ethoxide prepared from 0.6 g. of sodium and 50 ml. of ethanol. The mixture was refluxed for 6 hours, filtered hot, the filtrate evaporated to dryness *in vacuo*, and the residue dissolved in 150 ml. of water. The aqueous solution was successively percolated through columns of Amberlite Resin IRA-400 and IR-120. The percolate was evaporated to dryness *in vacuo* (bath temp. 40–45°) and the crystalline residue was recrystallized from a mixture of methanol and ether; yield 2.5 g.; m.p., 111–113°. Two additional recrystallizations elevated the melting point to 114–115°; yield after recrystallization: 1.2 g.

Anal. Calc'd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.29; N, 6.07. Found: C, 57.33; H, 8.13; N, 5.78.

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(7) General procedure of C. L. Stevens and W. Holland, *J. Org. Chem.*, **18**, 1112 (1953) for phosphorus tribromide-catalyzed bromination of primary and secondary nitriles.