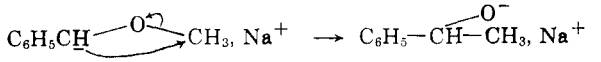
0° by an ice-salt bath. The reaction mixture became dark purple immediately and a vigorous, short-lived, exothermic reaction raised the internal temperature to 190°. A 38% yield of 1-phenylethanol was observed among the products upon gas chromatography.

It is felt that the results of this work are accomodated by the presently accepted mechanism[1,2] of the ether → carbinol rearrangement. Cleavage of benzyl methyl ether by sodium benzyl (step 1) may be followed by proton exchange with benzyl methyl ether (step 2). Internal displacement (step 3) produces the anion of the observed product.

$$C_6H_5CH_2OCH_3 + 2Na \longrightarrow C_6H_5CH_2^-,Na^+ + CH_3O^-,Na^+ \quad \text{(Step 1)}$$

$$C_6H_5CH_2^-,Na^+ + C_6H_5CH_2OCH_3 \rightleftharpoons C_6H_5CH_3 + C_6H_5C^-HOCH_3,Na^+ \quad \text{(Step 2)}$$



(Step 3)

While this mechanism does account qualitatively for the ultimate production of toluene although the solution is not an efficient source of benzyl anion for the scavenger benzophenone, the cause of the difference in the action of lithium (cleavage without rearrangement at −5°) and sodium (cleavage and rearrangement at 55° and higher) on benzyl methyl ether is not yet established.

EXPERIMENTAL

Columns for the gas chromatographic analyses were prepared as follows:

The silicone rubber packing was prepared by evaporative deposition of SE-30 Silicone Rubber[7] from chloroform solution onto four times its weight of Chromosorb W (60–80 mesh). The dry packing was introduced into a 6-ft. length of 0.25 in. O.D. copper tubing which was coiled and used in a Wilkens Aerograph Model A-90-C.

The Reoplex column was prepared by evaporative deposition of Reoplex 400[8] from chloroform solution onto four times its weight of Chromosorb W (60–80 mesh). The dry packing was suspended in water and the *p*H of the solution was adjusted to 7.4 by additions of 1% aqueous sodium carbonate and 1% aqueous acetic acid. The packing was dried at 110° for 2.5 hr. A test portion of the dry packing when resuspended in water gave a *p*H of 7.2. An 18-ft. copper column was employed in the determinations.

The benzyl methyl ether was distilled before use and had the constants: b.p. 93–94° (61 mm.); n_D^{20} 1.5013; water by Karl Fischer, 0.0167%. Infrared spectra were obtained with a Perkin-Elmer instrument, model 21.

Reaction of sodium with benzyl methyl ether. Freshly cut sodium cubes (6.0 g., 0.26 mole) were added to benzyl methyl ether (6.1 g., 0.5 mole). The mixture was stirred rapidly and blanketed with nitrogen throughout the reaction. Heat was applied to bring the internal temperature to 115° as rapidly as possible. A brief transition period occurred between 90 and 100° as the sodium melted and was thereafter present as finely dispersed globules. During this transition the pale yellow color of the reactants deepened and soon became purple-black. The internal temperature was maintained at 110–115° for 2 hr. at which time the sodium had disappeared. After cooling to room temperature, water (100 ml.) was added cautiously, the first several drops sufficing to discharge the purple color. The pale yellow organic layer was washed twice with saturated salt solution and dried over sodium sulfate. Filtration gave a pale yellow oil (37 g.) which was examined by gas chromatography on the Reoplex column at 150° and a flow of 50 cc./min., and on the silicon column at 238° and a flow of 30 cc./min. Three components were present: toluene (23%, 8.5 g.), unchanged benzyl methyl ether (61%, 22.5 g.), and 1-phenylethanol (15%, 5.5 g.). The identity of each component was established by its retention time on both columns and by observing the effect on the trace of adding a suspect component to the reaction mixture. By this method benzyl alcohol and 2-phenylethanol were shown to be absent from the products.

From a companion experiment the crude product was fractionated, and the infrared spectrum (neat) of the appropriate fraction was found to be that of 1-phenylethanol contaminated with benzyl methyl ether.

The reactions at lower temperatures were conducted in the same fashion except that the internal temperature was maintained at 50–60°.

Acknowledgment. The author wishes to thank Mr. Ronald Knight for the measurement of the infrared spectra, Mr. Aaron Kossoy for assistance and advice on the gas chromatographic analysis, and Mr. John Murray for his aid with the experimental portion of this work.

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(7) Obtained from the General Electric Co., Silicone Products Dept., Waterford, N. Y.

(8) Obtained from Wilkens Instrument and Research, Inc., Walnut Creek, Calif.

Derivatives of 1,3-Diazaspiro[4.5]decane

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Received February 22, 1961

Because of the interesting pharmacological properties of a number of 1-substituted 1,3-diazaspiro[4.5]dec-2-en-4-ones,[1] it became necessary to extend our work to the synthesis of other derivatives of the 1,3-diazaspiro[4.5]decane ring system.

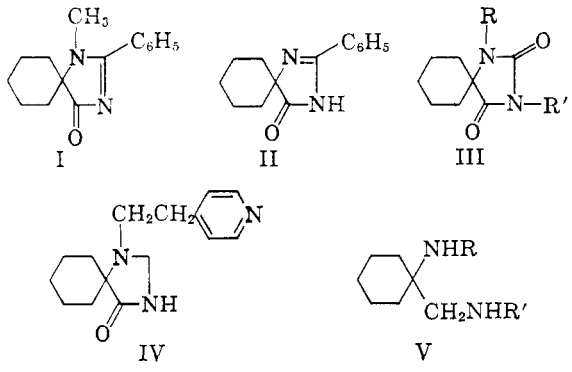
As starting materials for this investigation we selected appropriately substituted 1-aminocyclohexanecarboxamides which are readily accessible from their corresponding aminonitriles.[1] Reaction between 1-(methylamino)cyclohexanecarboxamide and benzoyl chloride resulted directly in the formation of 1-methyl-2-phenyl-1,3-diazaspiro[4.5]dec-2-en-4-one (I); the corresponding reaction with 1-aminocyclohexanecarboxamide[1] led to 2-phenyl-1,3-diazaspiro[4.5]dec-1-en-4-one (II) whose structural assignment to the class of 5(4*H*)imidazolones is based on its ultraviolet spectrum which exhibits peak absorption at 230 mμ (log ε 4.24) but no absorption in the 260 mμ –270 mμ region.

(1) E. Schipper and E. Chinery, *J. Org. Chem.*, **26**, in press.

A novel method, consisting of the treatment of 1-alkylaminocyclohexanecarboxamides or 1-alkylaminocyclohexanecarboxylates with nitrourea, was employed in the synthesis of several 1-substituted spirohydantoins (III) (R = alkyl, R = H). A 3-substituted hydantoin—3-[2-(4-pyridyl)ethyl]-1,3-diazaspiro[4.5]decane-2,4-dione (III. R = H, R′ = CH_2CH_2-(4-pyridyl)) was prepared by the pyridylethylation[2] of 1,3-diazaspiro[4.5]decan-2,4-dione.[3]

The reaction of α-aminoamides and formamide was shown previously[4] to result in the formation of 4-imidazolidones. When this procedure was applied to 1-[2-(4-pyridyl)ethylamino]cyclohexanecarboxamide[1] the pyridylethyl group was lost and 1-formyl-1,3-diazaspiro[4.5]decane-4-one[4] was isolated. The desired compound IV could be obtained, however, by catalytic hydrogenation of the corresponding spiroimidazolone.[1]

Finally, the synthesis of derivatives of 1,3-diazaspiro[4.5]decane-2-one was attempted. Lithium aluminum hydride reduction of 1-alkyl- and 1-aralkylaminocyclohexanecarboxamides furnished the diamines V (R = alkyl or aralkyl, R′ = H) but their reaction with ethylcarbonate did not lead to the expected spiroimidazolones. The reaction product consisted of aminourethanes (V) (R = alkyl or aralkyl, R′ = carbethoxy), which did not cyclize when subjected to heat (150°) or treatment with 10% sodium hydroxide.



EXPERIMENTAL[5a,b]

1-Methyl-2-phenyl-1,3-diazaspiro[4.5]dec-2-en-4-one (I). To a stirred solution containing 20 g. of 1-(methylamino)-cyclohexanecarboxamide,[6] 15 g. of pyridine and 150 ml. of chloroform there was added dropwise 25 g. of benzoyl chloride while the temperature was maintained at 10° by means of an ice bath. The solution was refluxed for 2 hr. and the solid was removed by filtration. The filtrate was evaporated to dryness and the residue was taken up in 100 ml. of benzene. The solution was washed with successive 200-ml. portions of 2*N* hydrochloric acid, 10% potassium carbonate, and water. The solvent was evaporated and the residue recrystallized from ethyl acetate. Yield, 16.5 g. (53%), m.p. 134–135°.

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.39; H, 7.54; N, 11.30.

2-Phenyl-1,3-diazaspiro[4.5]dec-1-en-4-one (II). This compound was prepared by the above procedure from 20 g. of 1-aminocyclohexanecarboxamide. Yield, 23.4 g. (56%), m.p. 143–144°.

Anal. Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.84; H, 7.22; N, 12.25.

1-Methyl-1,3-diazaspiro[4.5]decane-2,4-dione (III. R = CH_3; R′ = H). a. *From 1-(methylamino)cyclohexanecarboxamide.* A solution consisting of 62 g. of 1-(methylamino)-cyclohexanecarboxamide, 45 g. of nitrourea, and 500 ml. of water was heated at 70–80° for 2 hr. The solvent was removed under reduced pressure and the residue was taken up in 1 l. of xylene. The suspension was refluxed for 6 hr. The solvent was evaporated and the residue was recrystallized from water. Yield, 48 g. (66%), m.p. 175–176° (reported[7] m.p. 174°).

b. *From ethyl 1-(methylamino)cyclohexanecarboxylate.*[8] A solution containing 50 g. of ethyl 1-(methylamino)cyclohexanecarboxylate, 40 g. of nitrourea, 800 ml. of water, and 400 ml. of ethanol was heated at 70° for 2 hr. The solvents were evaporated under reduced pressure and the residue was recrystallized from water. Yield, 34 g. (69%), m.p. 174–175°.

1-(2-Diethylaminoethyl)-1,3-diazaspiro[4.5]decane-2,4-dione (III, R = $CH_2CH_2N(C_2H_5)_2$; R′ = H). A solution containing 10 g. of 1-(2-diethylaminoethylamino)cyclohexanecarboxamide,[1] 9 g. of nitrourea, 250 ml. of water, and 50 ml. of ethanol was heated at 70° for 2 hr. The solvents were evaporated and the residue was refluxed with 200 ml. of xylene. A precipitate was removed by filtration, the filtrate was condensed to dryness, and the residue triturated with pentane. The resulting solid was recrystallized from ethyl acetate. Yield, 6.4 g. (58%), m.p. 174–175°.

Anal. Calcd. for $C_{14}H_{25}N_3O_2$: C, 62.89; H, 9.43; N, 15.72. Found: C, 62.80; H, 9.37; N, 15.75.

3-[2-(4-Pyridyl)ethylamino]-1,3-diazaspiro[4.5]decane-2,4-dione (III. R = H, R′ = CH_2CH_2-(4-pyridyl)). A suspension consisting of 16.8 g. of 1,3-diazaspiro[4.5]decane-2,4-dione,[3] 10.8 g. of 4-vinylpyridine, 6 ml. of glacial acetic acid, and 35 ml. of absolute ethanol was refluxed for 4 days. The mixture was evaporated to dryness under reduced pressure and the residue triturated with 100 ml. of 1*N* potassium hydroxide. The insoluble portion was filtered off, washed with water, dried, and recrystallized from ethyl acetate–ethanol (8:2). Yield, 22.5 g. (82%), m.p. 207–208°.

Anal. Calcd. for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.74; H, 7.25; N, 15.57.

1-[2-(4-Pyridyl)ethylamino]-1,3-diazaspiro[4.5]decane-4-one (IV). A solution of 10 g. of 1-[2-(4-pyridyl)ethylamino]-1,3-diazaspiro[4.5]dec-2-en-4-one[1] in 100 ml. of 95% ethanol was subjected to hydrogenation at an initial pressure of 50 lb.; platinum on charcoal (5%) was employed as catalyst. After hydrogen uptake had ceased, the catalyst was filtered off and the solvent evaporated under reduced pressure. The residual solid was recrystallized from ether. Yield, 8.6 g. (84%), m.p. 172–173°.

Anal. Calcd. for $C_{15}H_{21}N_3O$: C, 69.46; H, 8.16; N, 16.21. Found: C, 69.47; H, 8.05; N, 15.99.

Reduction of 1-alkyl- and 1-aralkylcyclohexanecarboxamides. Into a Soxhlet thimble was placed 0.2 mole of the aminoamide and the material was extracted into a stirred and refluxing suspension of 15 g. of lithium aluminum hydride in 1 l. of ether. After the completed reaction (1–2 days) the excess hydride was destroyed with 25% sodium hydroxide. The

(2) H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 5434 (1955).

(3) H. T. Bucherer and V. A. Lieb, *J. prakt. Chem.*, **141**, 5 (1934).

(4) E. Schipper, *Chem. & Ind.*, 464 (1960).

(5)(a) All melting points are uncorrected. (b) Analyses by Mr. E. Hoffmann and staff.

(6) H. C. Carrington, *J. Chem. Soc.*, 1619 (1948).

(7) H. C. Carrington and W. S. Waring, *J. Chem. Soc.*, 354 (1950).

(8) E. Schipper and E. Chinery, *J. Org. Chem.*, in press (1961).

supernatant was decanted and distilled. The following diamines were prepared by this method:

1-Methylaminocyclohexanemethylamine (V. R = CH_3, R′ = H). Yield, 78%, b.p. 48–50°/0.07 mm., n_D^{25} 1.4843.

Anal. Calcd. for $C_8H_{18}N_2$: C, 67.55; H, 12.76; N, 19.70. Found: C, 67.80; H, 12.71; N, 19.45.

1-Benzylaminocyclohexanemethylamine (V. R = $CH_2C_6H_5$; R′ = H). Yield, 65%, b.p. 109–110°/0.09 mm., n_D^{24} 1.5392.

Anal. Calcd. for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16; N, 12.83. Found: C, 77.25; H, 10.07; N, 12.75.

1-(2-Diethylaminoethylamino)cyclohexanemethylamine (V. R = $CH_2CH_2N(C_2H_5)_2$; R′ = H). Yield, 53%, b.p. 87–90°/0.09 mm.

Anal. Calcd. for $C_{13}H_{29}N_3$: C, 68.66; H, 12.86; N, 18.48. Found: C, 68.54; H, 12.70; N, 18.60.

1-Methylamino-N-carbethoxycyclohexanemethylamine (V. R = CH_2; R′ = $COOC_2H_6$) *hydrochloride*. A solution consisting of 7 g. of V(R = CH_3, R′ = H) and 25 ml. of ethyl carbonate was refluxed for 3 days. The excess reagent was removed under reduced pressure and the residue was taken up in 100 ml. of ether. Saturation of the ethereal solution with hydrogen chloride gave a precipitate, which was extracted with ethyl acetate to yield, upon cooling, white needles. Yield, 4.4 g. (36%), m.p. 203–205°.

Anal. Calcd. for $C_{11}H_{23}ClN_2O_2$: C, 52.68; H, 9.24; N, 11.14. Found: C, 52.70; H, 9.28; N, 11.30.

1-Benzylamino-1-carbethoxyaminomethylcyclohexane (V. R = $CH_2C_6H_5$; R′ = $COOC_2H_5$) hydrochloride. The above procedure was applied to 9.2 g. of V (R = $CH_2C_5H_5$; R′ = H). The product was recrystallized from ethyl acetate. Yield, 5.8 g. (43%), m.p. 174–176°.

Anal. Calcd. for $C_{17}H_{27}ClN_2O_2$: C, 62.46; H, 8.33; N, 8.58. Found: C, 62.61; H, 8.30; N, 8.36.

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A Novel Ring System: 3,8-Diazabicyc[3.2.1]octane

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Received February 23, 1961

In view of the recent publication of Cignarella and Nathansohn[2] relating to the synthesis and reactions of 2,5-disubstituted pyrrolidines we wish to report, at the present time, our experiments conducted along similar lines.

During studies leading to *N*-substituted 2,5-bischloromethylpyrrolidines — compounds possessing potent adrenolytic acitivity[3]—it became necessary to reinvestigate the v. Braun-Seemann synthesis[4] of alkyl 2,5-pyrrolidinedicarboxylates. When methyl α,α'-dibromoadipate[4] and methylamine were condensed in a molar ratio of 1:3 and the reaction mixture was subjected to distillation through a heated three-foot Vigreux column three products could be isolated. These were (a) the expected diester I (R = R′ = CH_3, R″ = OCH_3), (b) a small quantity of a material which solidified on standing and melted at 114–115° and (c) the amido ester I (R = R′ = CH_3, R″ = $NHCH_3$) which constituted the major product of the reaction. When ethyl α,α'-dibromoadipate[4] was employed in place of the methyl ester, the diester I (R = CH_3, R′ = C_2H_5, R″ = OC_2H_5) was isolated as the primary product; in addition, the solid material, m.p. 114–115°, again was formed together with some higher boiling material not obtained pure, but probably consisting of the amido ester I (R = CH_3, R′ = C_2H_5, R″ = $NHCH_3$).

Elementary analysis and molecular weight determination of the solid fraction indicated it to be a derivative of the novel "3-azatropane" ring system—*i.e.*, 3,8-dimethyl-3,8-diazabicyclo[3.2.1]octane-2,4-dione (II. R = CH_3; X = O). This structural assignment is in accord with the observation that the compound is formed from either methyl or ethyl dibromoadipate and that it can be obtained in *ca.* 50% yield by heating the amido ester I (R = R′ = CH_3, R″ = $NHCH_3$) at 180°. Furthermore, the infrared spectrum in the carbonyl absorption region exhibits two peaks (at 1727 cm.$^{-1}$ and 1677 cm.$^{-1}$) typical of a cyclic diacylimide linkage.[5]

When II (R = CH_3, X = O) was subjected to lithium aluminum hydride reduction the dibasic 3,8-dimethyl-3,8-diazabicyclo[3.2.1]octane (II. R = CH_3, X = H_2) was obtained.

Application of the v. Braun-Seemann reaction[4] to a mixture of ethyl α,α'-dibromoadipate and β-diethylaminoethylamine produced none of the expected pyrrolidine diester; instead there could be isolated by careful fractionation of the reaction mixture the azatropane derivative II (R = $CH_2CH_2N(C_2H_5)_2$, X = O) and the diamide III (R = R′ = $CH_2CH_2N(C_2H_5)_2$). When *n*-butylamine and benzylamine were used as reactants, however, the major products consisted of the respective diesters I (R = *n* - C_4H_9 or C_7H_7, R′ = C_2H_5, R″ = OC_2H_5) and the amido esters I (R = *n*-C_4H_9, R′ = C_2H_5, R″ = NHC_4H_9-*n*) and I (R = C_7H_7, R′ = C_2H_5, R″ = NHC_7H_7). All attempts to convert these amido esters to the corresponding azatropanes failed as extensive resinification took place (compare also ref. 2).

These results, as well as experiments utilizing other amines,[3] indicate that the v. Braun-Seemann reaction[4]—particularly when carried out in the absence of a solvent—may lead to reaction products other than the expected pyrrolidine diesters. Whether the observed azatropanes are true reaction products or artifacts arising during the distil-

(1) Present address: William H. Rorer, Inc., Philadelphia, Pa.

(2) G. Cignarella and G. G. Nathansohn, *Gazz. chim. ital.*, 90, 1495 (1960).

(3) E. Schipper, W. R. Boehme, M. L. Graeme, E. Chinery, and E. Siegmund, *J. Med. Pharm. Chem.*, in press (1961).

(4) J. v. Braun and J. Seemann, *Ber.*, **56**, 1840 (1923).

(5)(a) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Wiley, New York, 1958, p. 221. (b) D. E. Ames and T. F. Grey, *J. Chem. Soc.*, 631 (1955).