[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

Heterocyclic Spiranes. Oxazolidines from (1-Aminocyclohexyl)methanol

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Received September 2, 1959

(1-Aminocyclohexyl)methanol (I) has been condensed with five aldehydes and a ketone, cyclohexanone. The reaction with ketones appears limited largely to cyclic ketones. Heterocyclic spiro oxazolidines or their derivatives were obtained from condensations with formaldehyde (II), benzaldehyde (IIa–IIc), *p*-nitrobenzaldehyde (IIId, IIIe), and cyclohexanone (VIIa–VIIc), dispiro oxazolidines being formed in the latter case. Structures were established by comparison of infrared and ultraviolet or molecular refraction data with appropriate analogs in the literature. Phthalaldehydic acid yielded an amino acid (tentatively formulated as IV, in the solid state), which isomerizes to a lactone (IVa) in chloroform solution. Dehydration of IV with benzoyl chloride yielded an interesting heterocyclic spiro oxazolidine lactam (V). Cinnamaldehyde yielded the Schiff base, (1-cinnamalaminocyclohexyl)methanol (VI). Several other new derivatives of (1-aminocyclohexyl)methanol are described.

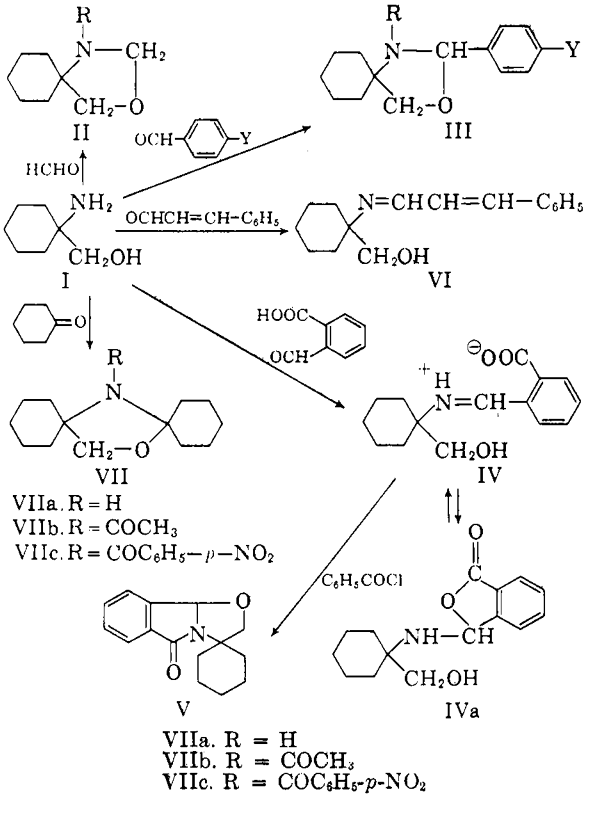
The synthesis of a number of heterocyclic spiro oxazolidines by the condensation of cyclohexanone and ethanolamine derivatives has been described previously.[2] In all of these cases the preformed cyclic component is contributed by the cyclohexanone. There appear to be only two recorded cases, however, of the synthesis of spiro oxazolidines in which the preformed cyclic component is contributed by the aminoalcohol. In one case, 17α-aminomethyl-Δ^5-androstene-3β,17β-diol condensed with acetone to yield an anhydro product, which was assumed to have the spiro oxazolidine structure.[3] In the other case, (1-aminoethyl)cyclohexanol condensed with cyclohexanone to give an anhydro product, to which the dispiro oxazolidine structure, 7-oxa-14-aza-15-methyldispiro[5.1.5.2]pentadecane, was assigned on the basis of molecular refraction data.[2,4]

In the present work another and more readily available cyclic amino alcohol, (1-aminocyclohexyl)methanol (I)[5,6] has been utilized in the synthesis of four new heterocyclic spiro oxazolidines (IIa, IIIa, IIId, V) or their derivatives, from aldehydes, and a dispiro oxazolidine (VIIa) and its derivatives, from cyclohexanone. The corresponding reaction with cinnamaldehyde yielded a Schiff base condensation product, (1-cinnamalaminocyclohexyl)methanol (VI). In general, the method of azeotropic removal of water with benzene was employed.[7]

The oily formaldehyde product is assumed to have the spiro oxazolidine structure IIa by analogy with the product from formaldehyde and 3-amino-2-methyl-2-butanol, which has been shown by infrared and molecular refraction data to be in the oxazolidine form, with a slight amount of the Schiff base.[2,4] The benzoyl derivative is assigned the spiro oxazolidine structure IIb because its infrared spectrum contains only an amide-type carbonyl band and has no OH or NH stretching bands.

IIa. R = H
IIb. R = COC_6H_5

IIIa. R = Y = H
IIIb. R = COC_6H_5, Y = H
IIIc. $CONHC_6H_5$, Y = H
IIId. R = H, Y = NO_2
IIIe. R = COC_6H_5, Y = NO_2



VIIa. R = H
VIIb. R = $COCH_3$
VIIc. R = COC_6H_5-*p*-NO_2

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[1] Taken in part from the senior thesis of Roy A. Johnson, University of Minnesota, 1958–59, and from his work as a Research Corporation Research Assistant, summer 1959. We are indebted to the Research Corporation for a Frederick Gardner Cottrell grant which supported a part of this work.

[2] E. D. Bergmann, *Chem. Revs.*, **53**, 309 (1953).

[3] H. Heusser, P. T. Herzig, A. Fürst, and P. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).

[4] E. D. Bergmann, E. Zimkin, and S. Pinchas, *Rec. trav. chim.*, **71**, 168 (1952).

[5] W. E. Noland, J. F. Kneller, and D. E. Rice, *J. Org. Chem.*, **22**, 695 (1957), and references cited therein.

[6] O. v. Schickh and G. Stochdorph (to Badische Anilin- und Soda-Fabrik Akt.-Ges.) German Patent **860,945**, Dec. 29, 1952 (Cl. 12o, 25) [*Chem. Abstr.*, **50**, 4206 (1956)].

[7] A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.*, **64**, 1503 (1942).

The oily benzaldehyde product, as was the case with the 3-amino-2-methyl-2-butanol product,[2,4,8] appears to be a mixture of the two possible isomers. For the sake of brevity, only the oxazolidine structure IIIa has been shown in the reaction chart. The benzoyl derivative is assigned the spiro oxazolidine structure IIIb because its infrared spectrum contains only an amide-type carbonyl band and has no OH or NH stretching bands. The absence of any ultraviolet absorption maximum is also consistent with the benzamide-type structure IIIb and eliminates the possible presence of the strongly absorbing Schiff base, which would be present in the isomeric structure, (1-benzalaminocyclohexyl)-methyl benzoate. For example, 3-benzalamino-2-methyl-2-butanol has the typical Schiff base maximum at 245 mμ (log ϵ 4.01).[8] The phenylurea derivative is also assigned a spiro oxazolidine structure IIIc. While the position of the carbonyl band in the infrared spectrum does not permit a clear-cut distinction between the oxazolidine and Schiff base structures, the principal ultraviolet absorption maximum in ethanol at 239 mμ (log ϵ 4.31) is at too low a wave length for a Schiff base (245[8]–247[9] mμ) and too high a wave length for an *N*-phenylcarbamate ester, a system which would also be present in the phenyl isocyanate derivative of the Schiff base form. For example, isopropyl and *n*-hexyl *N*-phenylcarbamate have their principal absorption maximum at 235–236 mμ (log ϵ 4.23).[10] On the other hand, the ultraviolet absorption maximum of an analogous *N*-phenylurea, 1,1-diethyl-3-phenylurea, at 239–241 mμ (log ϵ 4.26),[10] is in good agreement with that of our derivative (IIIc).

Both the *p*-nitrobenzaldehyde product (IIId) and its benzoyl derivative (IIIe), have spiro oxazolidine structures, in contrast to the product from ethanolamine and *p*-nitrobenzaldehyde, which has been shown to be in the open, Schiff base form.[2,4] The infrared spectra of IIId and IIIe have no band in the C=N region, such as that present at 1654 cm.$^{-1}$ in 3-(4-nitrobenzalamino)-2-methyl-2-butanol,[4] thus excluding the Schiff base structure. The benzoyl derivative (IIIe) has only an amide-type carbonyl band, thus confirming the oxazolidine structure for it. Since compounds IIId and IIIe have very similar ultraviolet spectra, they must both be oxazolidines. Taken by themselves, the wave lengths of the ultraviolet absorption maxima, at 267 (log ϵ 4.04) in IIId and 265 mμ (3.96) in IIIe, allow no clear basis for distinction between the oxazolidine and Schiff base structures since *p*-nitrotoluene, a model compound for the oxazolidine structures, has a maximum at 273 mμ (3.98),[10] whereas the condensation product of *p*-nitroacetophenone and 3-amino-2-methyl-2-butanol, a model Schiff base for this system, has maxima at 275 (4.07) and 235 (3.52).[8]

In what is apparently the first example of the reaction of an amino alcohol with phthalaldehydic acid, (1-aminocyclohexyl)methanol gave an amino acid, obtained in dimorphic forms, m.p. 133–136° and 147–150°, having a neutralization equivalent corresponding to a 1:1 condensation product. The zwitterion form of the Schiff base structure (IV) is tentatively assigned to the crystalline amino acid because of its infrared spectrum in Nujol. The stronger band at 1634 cm.$^{-1}$ is tentatively assigned to the C=N structure and the band at 1560 cm.$^{-1}$ to the antisymmetrical stretching frequency of the carbonyl group of the ionized carboxyl group. In chloroform solution these two bands disappear and are replaced by a strong γ-lactone carbonyl band at 1754 cm.$^{-1}$, indicating that the amino acid has isomerized to the phthalide form (IVa). Phthalide itself has the carbonyl band at 1770 cm.$^{-1}$ in carbon tetrachloride solution.[11] The ultraviolet spectrum in ethanol solution is again suggestive of the phthalide (IVa) or oxazolidine form. The characteristic Schiff base maximum at about 245 mμ (possibly shifted to a higher wave length by conjugation with the *o*-carboxyl group) appears to be lacking. Instead, there are two maxima, the high intensity one at 237 (log ϵ 3.92), and the other at 294 mμ (3.15). These maxima are at higher wave lengths and intensities, but are similar in distance apart and in relative intensities to those of *o*-toluic acid at 228 (log ϵ 3.71) and 279 mμ (2.86),[12] or of phthalide at 227 (4.00), 273 (3.24), and 280 (3.22).[10]

The reaction of phthalaldehydic acid with amino alcohols may provide interesting opportunities in organic synthesis. For example, the amino acid IV upon dehydration with benzoyl chloride in pyridine yielded the spiro lactam V. This lactam has a strong γ-lactam carbonyl band in the infrared (at 1691 cm.$^{-1}$ in Nujol) and no NH stretching absorption. The model compound, phthalimidine, has a strong carbonyl band at 1700 cm.$^{-1}$ in carbon tetrachloride.[13] The lactam (V) is resistant to alkaline hydrolysis in aqueous ethanol.

In contrast to the mixture of isomers obtained with benzaldehyde, and the pure oxazolidine obtained with *p*-nitrobenzaldehyde, cinnamaldehyde gave the Schiff base, (1-cinnamalaminocyclohexyl)-methanol (VI), as the only crystalline product. The infrared spectrum in Nujol is in good agreement with the Schiff base structure (VI). The ultraviolet spectrum in ethanol is also in good agreement, since its long wave length maximum

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(8) E. D. Bergmann, Y. Hirshberg, S. Pinchas, and E. Zimkin, *Rec. trav. chim.*, **71**, 192 (1952).

(9) G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, **73**, 3923 (1951).

(10) W. A. Schroeder, P. E. Wilcox, K. N. Trueblood, and A. O. Dekker, *Anal. Chem.*, **23**, 1740 (1951).

(11) F. Pristera, *Anal. Chem.*, **25**, 855 (1953).

(12) C. M. Moser and A. I. Kohlenberg, *J. Chem. Soc.*, 804 (1951).

(13) W. Theilacker and W. Schmidt, *Ann.*, **597**, 95 (1955).

occurs at 287 (log ϵ 4.40), whereas that of the dicinnamyl derivative of ethylenediamine occurs at 282 mμ (log $\epsilon/2$ 4.44).[14] In contrast, the high intensity band of β-methylstyrene, a model compound for the oxazolidine structure, occurs at 251 mμ (log ϵ 4.21).[15] The formation of the Schiff base from cinnamaldehyde is consistent with the generalization that increased conjugation with the C=N group, such as that in the products from α,β-unsaturated aldehydes,[2,4] tends to favor the Schiff base form.

Water collected rapidly in the trap during all of the condensations with aldehydes; the reactions were probably complete within an hour, although refluxing was usually continued for a longer time. In contrast, the condensation with the ketone, cyclohexanone, was much slower and required several hours for all of the water to be collected. The liquid product from cyclohexanone has the dispiro oxazolidine structure VIIIa. The only previous report of a dispiro oxazolidine prepared by a similar method is that from (1-aminoethyl)-cyclohexanol and cyclohexanone.[2,4] Our dispiro oxazolidine (VIIa) has a molecular refraction of 60.346 at 32°. This value is in excellent agreement with that for the oxazolidine, of 60.379 at 30°, calculated from the Eisenlohr atomic refractions[4,16] and taking into account the average depression of 0.50 for the oxazolidine ring.[4,7] The Schiff base structure is excluded because of the lack of a C=N band in the infrared spectrum and because the calculated molecular refraction of 62.359 at 30° is too high. Oxazolidine structures for the acetyl (VIIb) and p-nitrobenzoyl (VIIc) derivatives of the dispiro oxazolidine are confirmed by the presence of amide carbonyl bands in the infrared.

The reaction of (1-aminocyclohexyl)methanol with ketones appears to be restricted to the relatively unhindered cyclic ketones and, possibly, to reactive ketones such as pyruvic acid. Acetone does not appear to react; when an equimolar solution of acetone and (1-aminocyclohexyl)methanol in benzene was refluxed for eighteen hours before removal of the benzene, the residual oil yielded a single benzoyl derivative, (1-benzamidocyclohexyl)methanol, derived from the starting material. Likewise, acetophenone and diethyl ketone do not react; only negligible amounts of water were collected by azeotropic removal with benzene.

During the course of this work several other new derivatives of (1-aminocyclohexyl)methanol were prepared. Included among these, besides the benzamide, are the di-p-nitrobenzoyl derivative, and the benzoate and carbonate salts. (1-Aminocyclohexyl)-methanol is notably "carbodioxiphilic";[17] it absorbs carbon dioxide readily, both in the presence and absence of water.

EXPERIMENTAL

Melting points were determined on a calibrated Kofler micro hot stage.

1-Aza-3-oxaspiro[4.5]decane (IIa). A mixture of (1-aminocyclohexyl)methanol[5] (3.20 g., 0.0248 mole), aqueous 37% formalin (10 cc., 0.12 mole formaldehyde), and benzene (50 cc.) was refluxed for 9 hr. A calibrated constant water separator (Dean and Stark trap) was then attached and refluxing was continued. The water (about 13.5 cc.) came over during the first hour but refluxing was continued for a total of 6 more hr. The benzene was then distilled and a large relatively volatile fraction was removed at 75–82° (5 mm.), leaving a light yellow residual oil (1.73 g., 0.0123 mole, 50%). This oil was converted to its benzoyl derivative without distillation or further purification.

1-Benzoaza-3-oxaspiro[4.5]decane (IIb; *benzamide of* IIa). By the Schotten-Baumann method, to a mixture of crude 1-aza-3-oxaspiro[4.5]decane (0.8 g., 0.0057 mole), benzoyl chloride (0.8 g., 0.0057 mole), and water (10 cc.) was added aqueous 20% sodium hydroxide (7 cc.). The mixture was shaken and a white crystalline solid (1.23 g., 0.0050 mole, 88%), m.p. 115–130°, formed rapidly. Four recrystallizations from ethanol-water yielded colorless flakes, m.p. 127–129°; $\nu_{\text{OH or NH}}$ none; $\nu_{\text{C=O}}$ 1639 in CS_2, 1634 in CCl_4, 1622 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{15}H_{19}NO_2$ (245.31): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.27; H, 7.72; N, 5.64.

Mixture of (1-benzalaminocyclohexyl)methanol and 1-aza-2-phenyl-3-oxaspiro[4.5]decane (IIIa). A solution of (1-aminocyclohexyl)methanol[5] (10.0 g., 0.0774 mole) and benzaldehyde (16.4 g., 0.154 mole) in undried benzene (75 cc.) was refluxed under a calibrated constant water separator until the distillation of water was complete. Water began to collect immediately; after 30 min. 1.0 cc. (72%) had collected and at the end of the 5-hr. reflux period a total of 1.6 cc. (115%) had collected in the trap. The benzene was distilled and the excess benzaldehyde was removed at 50–55° (4 mm.). The residual light yellow oil (88%) was distilled, giving a pale yellow fraction (12.34 g., 0.0569 mole, 74%), b.p. 127–132° (2 mm.), n_D^{26} 1.5413. Redistillation yielded a very pale yellow analytical sample, b.p. 128–129° (2 mm.), n_D^{25} 1.5415. The odor of the sample, as well as the infrared spectrum, indicated contamination by both starting materials, which were not successfully separated by repeated distillation; ν_{OH} 3430 (shoulder); ν_{NH} 3310; $\nu_{\text{C=O}}$ 1704 (benzaldehyde); $\nu_{\text{C=N}}$ 1645 cm.$^{-1}$ on the liquid. The C=N band, of medium intensity, indicated the presence of the open form of the product, (1-benzalaminocyclohexyl)methanol.

Anal. Calcd. for $C_{14}H_{19}NO$ (217.30): C, 77.38; H, 8.81. Found: C, 76.78; H, 8.85.

The benzaldehyde contaminant in the sample appears to undergo air oxidation to benzoic acid, as evidenced by precipitation of 1-(hydroxymethyl)cyclohexylammonium benzoate in the samples fairly soon after distillation and analysis. The melting point of the precipitate was undepressed upon admixture with an authentic sample of this benzoate salt.

The crude oil resulting from removal of the benzene and excess benzaldehyde was used for the preparation of crystalline derivatives without distillation or other purification. It was shown, however, that the same benzoyl derivative was

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(14) L. N. Ferguson and G. E. K. Branch, *J. Am. Chem. Soc.*, **66**, 1467 (1944).

(15) American Petroleum Institute Research Project 44. Carnegie Institute of Technology. Catalog of Ultraviolet Spectral Data. Serial No. 122, contributed by The Dow Chemical Co., Dec. 31, 1945.

(16) K. Fajans in A. Weissberger, *Physical Methods of Organic Chemistry*, Vol. 1, Part 2, Interscience Publishers, Inc., New York, N. Y., 1949, p. 1163.

(17) W. E. Parham, W. T. Hunter, and R. Hanson, *J. Am. Chem. Soc.*, **73**, 5068 (1951).

obtained from a distilled sample of the oil; after two recrystallizations from ethanol-water, the benzoyl derivative melted at 134–136°, which was undepressed upon admixture of the sample with that prepared as described in the following section.

The oil was immiscible with water and surprisingly resistant to hydrolysis. A sample which had been overlaid with water for 2 weeks had the odor of benzaldehyde, but readily gave the benzoyl derivative under the conditions of the Schotten-Baumann reaction. After two recrystallizations from ethanol-water, the benzoyl derivative melted at 133–136°, which was undepressed upon admixture of the sample with that prepared as described in the following section.

1-Benzoaza-2-phenyl-3-oxaspiro[4.5]decane (IIIb; *benzamide of* IIIa). By the Schotten-Baumann method, to a mixture of crude (1-benzalaminocyclohexyl)methanol and 1-aza-2-phenyl-3-oxaspiro[4,5]decane (1.0 g., 0.0046 mole), benzoyl chloride (0.8 g., 0.006 mole), and water (10 cc.) was added aqueous 20% sodium hydroxide (7 cc.) over a period of 5 min., with vigorous shaking. The mixture was intermittently warmed gently on the steam bath and shaken for 5 more min. The coagulated yellowish mass was then crystallized from ethanol-water, giving light yellowish plates (0.54 g., 0.0017 mole, 37%), m.p. 126–136°. Three recrystallizations from ethanol-water yielded colorless plates, m.p. 134–136.5°. The ultraviolet spectrum in 95% ethanol shows only rising end absorption (at 220 mμ, log ϵ is 3.99 and at 215, 4.05); $\nu_{OH\text{ or }NH}$ none; $\nu_{C=O}$ 1640 in CS_2, 1645 in CCl_4, 1628 in $CHCl_3$, 1629 in a KBr disk, 1627 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{21}H_{23}NO_2$ (321.40): C, 78.47; H, 7.21; N, 4.36. Found: C, 78.56; H, 7.32; N, 4.25.

1-(Phenylcarbamoaza)-2-phenyl-3-oxaspiro[4.5]decane (IIIc; *phenylurea derivative of* IIIa) was obtained after five recrystallizations from light petroleum (b.p. 60–68°) as colorless, chunky crystals, m.p. 124–127°; λ_{max} in 95% C_2H_5OH: 239 mμ (log ϵ 4.31), with inflections at 268 (3.23), 272 (3.17), 281 (3.10); ν_{NH} 3390 in CS_2 and CCl_4, 3400 in $CHCl_3$, 3380 in Nujol; $\nu_{C=O}$ 1672 in CS_2, 1682 in CCl_4, ~1667 in $CHCl_3$, 1675 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$ (336.42): C, 74.97; H, 7.19; N, 8.33. Found: C, 75.14; H, 7.19; N, 8.46.

1-Aza-2-(4-nitrophenyl)-3-oxaspiro[4.5]decane (IIId). A solution of (1-aminocyclohexyl)methanol[4] (4.00 g., 0.0310 mole) and *p*-nitrobenzaldehyde (4.70 g., 0.0311 mole) in undried benzene (75 cc.) was refluxed under a calibrated constant water separator until the distillation of water was complete. Water began to collect immediately; at the end of the 2.5-hr. reflux period 0.62 cc. (111%) had collected. The benzene was distilled and the residue was dried at aspirator pressure, leaving a brown powder (8.20 g.). Crystallization from ethanol-water gave light yellowish flakes (5.41 g., 0.0206 mole, 66%), m.p. 73–77°. Four recrystallizations from ethanol-water yielded 1-aza-2-(4-nitrophenyl)-3-oxaspiro-[4,5]decane as colorless flakes, m.p. 77–79°; λ_{max} in 95% C_2H_5OH: 267 mμ (log ϵ 4.04); ν_{NH} 3270 in CS_2, 3280 in CCl_4, 3270 in Nujol; ν_{NO_2} 1347 in CS_2, 1528, 1349 in CCl_4, 1516, 1348 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{18}N_2O_3$ (262.30): C, 64.10; H, 6.92; N, 10.68. Found: mol. wt. (Rast), 293; C, 63.88; H, 7.13; N, 10.73.

1-Benzoaza-2-(4-nitrophenyl)-3-oxaspiro[4.5]decane (IIIe; *benzamide of* IIId) was obtained by the Schotten-Baumann reaction in 23% yield, m.p. 163–166°, after two recrystallizations. A final recrystallization from ethanol-water yielded colorless, shiny plates, m.p. 163–165°; λ_{max} in 95% C_2H_5OH: 265 mμ (log ϵ 3.96). $\nu_{OH\text{ or }NH}$ none; $\nu_{C=O}$ 1625; ν_{NO_2} 1520, 1350 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{21}H_{22}N_2O_4$ (366.40): C, 68.83; H, 6.05; N, 7.65. Found: C, 68.94; H, 6.01; N, 7.35.

Zwitterion form of (1-(2-carboxybenzal)aminocyclohexyl)-methanol (IV). A solution of (1-aminocyclohexyl)methanol[5] (6.40 g., 0.0495 mole) and phthalaldehydic acid (7.50 g., 0.0499 mole) in undried benzene (100 cc.) was refluxed under a calibrated constant water separator until the distillation of water was complete. Within 20 min. 1.0 cc. of water had collected; at the end of the 7.5-hr. reflux period 1.20 cc. (134%) had collected. After the solution had been set aside overnight, a white precipitate was present, which did not redissolve when the benzene was warmed for distillation. The benzene was distilled under aspirator vacuum. The residual solid (~12 g., 0.046 mole, 93%) dissolved slowly in chloroform. Five recrystallizations from chloroform–light petroleum (b.p. 60–68°), yielded white crystals, m.p. 133–136°; λ_{max} in 95% C_2H_5OH: 237 mμ (log ϵ 3.92), 294 (3.15); $\nu_{OH\text{ or }NH}$ 3100; $\nu_{C=N}$ 1634; $\nu_{C=O}$ 1560 cm.$^{-1}$ in Nujol; in $CHCl_3$: $\nu_{C=O}$ 1754 cm.$^{-1}$; $\nu_{C=N}$ none.

Anal. Calcd. for $C_{15}H_{19}NO_3$ (261.31): C, 68.94; H, 7.33; N, 5.36. Found: acid neut. equiv. 267, 275, 273, av. 272; C, 69.19; H, 7.70; N, 5.46.

The compound was also obtained from the same solvent pair in admixture with, or wholly in a higher melting dimorphic form, m.p. 147–150°.

Anal. Found: C, 68.94; H, 7.35; N, 5.26.

The two dimorphic forms had identical infrared spectra in Nujol and were shown to be interconvertible.

Spiro[2,3-oxazolo(2,3-a)isoindol-5-one-3,1′-hexane] (V). Benzoyl chloride (1.08 g., 0.0077 mole) was added to a solution of (1-(2-carboxybenzal)aminocyclohexyl)methanol (1.00 g., 0.00382 mole) in pyridine (15 cc.). The resulting solution was warmed at about 75° for 45 min. and then poured into ice water, causing the separation of a light yellow oil. The mixture was stirred and crystals (0.69 g., 0.00284 mole, 74%), m.p. 88–100°, formed over a period of an hour. The compound can be recrystallized, if desired, from ethanol-water. From separate solutions of water containing a small amount of pyridine, the compound was obtained in two forms, m.p. 80.5–82°, and m.p. 98–100°. The lower melting form was converted to the higher melting form after heating *in vacuo* at 56°; λ_{max} in 95% C_2H_5OH: 225 mμ (log ϵ 3.94), 230 inflection (3.89), 245 (3.69), 280 inflection (3.17). ν_{NH} none; $\nu_{C=O}$ 1691 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{15}H_{17}NO_2$ (243.29): C, 74.05; H, 7.04; N, 5.76. Found: lower melting form (after heating), C, 74.11; H, 7.15; N, 5.67; higher melting form, mol. wt. (Rast), 246; C, 73.58; H, 7.25; N, 5.54.

(1-Cinnamalaminocyclohexyl)methanol (VI). A solution of (1-aminocyclohexyl)methanol[5] (3.20 g., 0.0247 mole) and cinnamaldehyde (9.00 g., 0.0680 mole) in undried benzene (60 cc.) was refluxed under a calibrated constant water separator until the distillation of water was complete. Water began to collect immediately; at the end of the 2.5-hr. reflux period 0.60 cc. (135%) had collected. The dark yellow solution turned strawberry red upon being set aside overnight. Excess benzene was removed at aspirator pressure and cinnamaldehyde was removed at 95–105° (3 mm.). The viscous, dark red residue was dissolved in benzene (15 cc.), causing immediate separation of crystals. These crystals were washed with a little benzene to remove contaminating red oil, and recrystallized from benzene–light petroleum (b.p. 60–68°), giving light yellowish needles (1.10 g., 0.00453 mole, 18%), m.p. 90–93°. Three more recrystallizations from benzene–light petroleum (b.p. 60–68°) yielded (1-cinnamalaminocyclohexyl)methanol as colorless needles, m.p. 96–98°; λ_{max} in 95% C_2H_5OH: 220 mμ (log (ϵ 4.07), 225 (4.06), 287 (4.40); ν_{OH} 3160 in Nujol; $\nu_{C=N}$ 1631 in CS_2, 1633 in CCl_4, 1634 in Nujol. $\nu_{C=C}$ 1617 in CCl_4, 1615 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{16}H_{21}NO$ (243.34): C, 78.97; H, 8.70; N, 5.76. Found: C, 79.24; H, 8.75; N, 5.76.

An attempt to prepare a benzoyl derivative by the Schotten-Baumann method gave no crystalline product.

7-Oxa-15-azadispiro[5.2.5.1]pentadecane (VIIa). A solution of (1-aminocyclohexyl)methanol[5] (20.0 g., 0.155 mole) and cyclohexanone (30.4 g., 0.310 mole) in undried benzene (100 cc.) was refluxed under a calibrated constant water separator until the distillation of water was complete. Water collected slowly; at the end of the 9-hr. reflux period 3.7 cc. (132%) of water had collected. The benzene was distilled, the excess cyclohexanone was removed at 35–38° (2 mm.), and then the main fraction distilled as a light yellow oil (28.92 g., 0.138 mole, 89%), b.p. 98–104° (2 mm.), $n_D^{27.4}$ 1.4913. Redistillation yielded 7-oxa-15-azadispiro-[5,2,5,1]-pentadecane as a colorless oil, b.p. 97–99° (2 mm.), $n_D^{27.4}$ 1.4915, n_D^{32} 1.4893, d_4^{32} 1.0002; ν_{NH} 3310 (very faint) cm.$^{-1}$, $\nu_{C=N}$ none; on the oil.

Anal. Calcd. for $C_{13}H_{23}NO$ (209.32): C, 74.59; H, 11.08; N, 6.69. Found: C, 74.85; H, 11.56; N, 7.08.

The benzoyl derivative tended to oil out of ethanol-water solution and did not crystallize well.

7-Oxa-15-azadispiro[5.2.5.1]pentadecane hydrochloride (*hydrochloride of* VIIa). Hydrogen chloride gas was passed into a solution of 7-oxa-15-azadispiro[5,2,5,1]pentadecane (2.00 g., 0.0096 mole) in dry ether (50 cc.), causing precipitation of fine, colorless platelets (1.88 g., 0.0077 mole, 80%). These crystals appear to change form at 180–190° and melt with sublimation at 204–207°; $\nu_{NH_2^+}$ 2740, 2590, 2460, 2370, 2090, 1586 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{13}H_{23}NO \cdot HCl$ (245.79): Cl, 14.42. Found: Cl, 14.62, 14.66, 14.56, 14.65, av. 14.62.

7-Oxa-15-acetoazadispiro[5.2.5.1]pentadecane (VIIb, *acetamide of* VIIa). A solution of 7-oxa-15-azadispiro[5,2,5,1]-pentadecane (2.00 g., 0.00957 mole) in acetic anhydride (18.5 g., 0.181 mole) was warmed for 3.25 hr. and then the yellow solution was poured into ice water (50 cc.). The resulting mixture was stirred occasionally, causing the yellow oil to crystallize slowly as colorless plates (1.01 g., 0.00402 mole, 42%), m.p. 119–124°. Five recrystallizations from acetone-water yielded colorless plates, m.p. 122–124°; $\nu_{OH\ or\ NH}$ none; $\nu_{C=O}$ 1634 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{15}H_{25}NO_2$ (251.36): C, 71.67; H, 10.03; N, 5.57. Found: C, 71.76; H, 9.96; N, 5.39.

(*7-Oxa-15-(4-nitrobenzoaza)dispiro[5.2.5.1]pentadecane* (VIIc; *p-nitrobenzamide of* VIIa). A solution of 7-oxa-15-azadispiro[5,2,5,1]pentadecane (2.00 g., 0.0096 mole) and *p*-nitrobenzoyl chloride (1.76 g., 0.0095 mole) in pyridine (15 cc.) was warmed on a steam bath for 60 min. The deep red solution was poured into ice water, causing precipitation of a light brown solid (2.80 g.), m.p. 100–120°. Five recrystallizations alternately from ethanol-water and acetone-water yielded colorless, rectangular crystals, m.p. 175–178°; $\nu_{OH\ or\ NH}$ none; $\nu_{C=O}$ 1630; ν_{NO_2} 1524, 1349 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{20}H_{26}N_2O_4$ (358.42): C, 67.02; H, 7.31; N, 7.82. Found: C, 66.94; H, 7.45; N, 8.01.

(*1-Benzamidocyclohexyl)methanol* (*benzamide of* I). By the Schotten-Baumann method, to a mixture of (1-aminocyclohexyl)methanol[5] (1.0 g., 0.0077 mole), benzoyl chloride (1.1 g., 0.0078 mole) and water (10 cc.) was added aqueous 20% sodium hydroxide as needed to keep the mixture basic to litmus. The resulting precipitate was dissolved in methylene chloride and reprecipitated by the addition of light petroleum (b.p. 60–68°). The precipitate (1.26 g., 0.0054 mole, 70%), m.p. 110–120° was recrystallized five times from methylene chloride–light petroleum (b.p. 60–68°), yielding colorless needles, m.p. 118–122°; $\nu_{NH,OH}$ 3420, 3320, in $CHCl_3$, 3260, 3050, 1554 in Nujol; $\nu_{C=O}$ 1640 cm.$^{-1}$ in $CHCl_3$ and in Nujol.

Anal. Calcd. for $C_{14}H_{19}NO_2$ (233.30): C, 72.07; H, 8.21; N, 6.00. Found: C, 72.19; H, 8.35; N, 6.05.

(*1-p-Nitrobenzamidocyclohexyl)methyl p-nitrobenzoate di-p-nitrobenzoyl derivative of* I) was obtained by the Schotten-Baumann reaction, after recrystallization from acetone-ethanol as colorless crystals, m.p. 193–195.5°; ν_{NH} 3380; $\nu_{C=O}$ 1714, 1663; ν_{NO_2} 1523, 1353 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{21}H_{21}N_3O_7$ (427.40): C, 59.01; H, 4.95; N, 9.83. Found: C, 59.16; H, 4.97; N, 9.98.

1-(Hydroxymethyl)cyclohexylammonium benzoate (*benzoate salt of* I) was obtained after recrystallization from methylene chloride as colorless needles, m.p. 159–160°; ν_{OH} 3310; $\nu_{NH_3^+}$ 2330, 2120, 1645; $\nu_{C=O}$ 1564 (shoulder), 1550, 1400 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{21}NO_3$ (251.32): C, 66.90; H, 8.42; N, 5.57. Found: C, 66.50; H, 8.24; N, 5.51.

Bis[1-(hydroxymethyl)cyclohexylammonium]carbonate (*carbonate salt of* I). Carbon dioxide gas was passed through a solution of (1-aminocyclohexyl)methanol[5] (2.00 g., 0.0155 mole) in water (5 cc.) for 30 min., forming a white powder (1.85 g.), m.p. 78–103°. Two washings with benzene yielded a sample (1.00 g., 0.0031 mole, 40%), m.p. 90–96°; $\nu_{NH_3^+}$ 2140, 1618; $\nu_{C=O}$ 1576, 1378 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{15}H_{32}N_2O_5$ (320.42): C, 56.22; H, 10.07; N, 8.74. Found: C, 56.83; H, 10.05; N, 8.55.

Addition of a saturated solution of barium hydroxide to an aqueous solution of the sample resulted in immediate formation of a white precipitate.

When carbon dioxide gas was passed through a solution of (1-aminocyclohexyl)methanol[5] (2.00 g., 0.0155 mole) in dry benzene (10 cc.) for 20 min., a white powder (1.60 g.), m.p. ~67–69° precipitated. This precipitate had an elemental composition resembling a mixture of the carbamide and carbamate, $RNHCONHR \cdot RNHCOO^{-}H_3\overset{+}{N}R$, where $R = C_7H_{13}O$.

Anal. Calcd. for $C_{30}H_{58}N_4O_7$ (596.80): C, 60.37; H, 9.80; N, 9.39. Found: C, 61.14; H, 10.42; N, 9.49.

In contrast to the immediate formation of a precipitate with the carbonate, addition of a saturated solution of barium hydroxide to a freshly prepared aqueous solution of the mixture prepared in the absence of water resulted in formation of a heavy flocculent white precipitate within 2–3 min.

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