evaporated and the residue distilled at reduced pressure through a 1″ × 14″ Vigreux column. Obtained were 16 g. of material, probably 4-chlorocyclohexene, b.p. 40–45° (13 mm.) and 21 g. (38% of theoretical) of *cis*-1,4-dichlorocyclohexane, b.p. 80–81° (13 mm.). Redistillation gave a sample having the following properties: m.p. 18°; b.p. 80.3° (12.5 mm.), 96° (25 mm.), 113.2° (50 mm.), 133° (100 mm., dec.), 193° (756.5 mm., dec.); n^{20}_D 1.4942, n^{25}_D 1.4920; d^{20}_4 1.1900, d^{25}_4 1.1847.

Anal. Calcd. for $C_6H_{10}Cl_2$: Cl, 46.33; mol. ref., 37.44. Found: Cl, 46.49; mol. ref., 37.45.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF SOUTH CAROLINA
COLUMBIA, S. C.

Trifunctional Aminocyclanols. Synthesis of 3-Aminocyclohexanediol-1,2

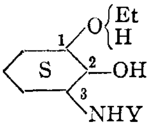
BY G. E. MCCASLAND, T. J. MATCHETT AND MARSHA HOLLANDER

RECEIVED JANUARY 30, 1952

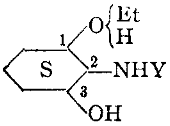
Through previous studies[1] on 2-aminocyclanols and 2-aminocyclohexanepentols (inosamines) we became interested in the synthesis of alicyclic compounds having three neighboring amino and/or hydroxy functional groups. Of the cyclohexane derivatives with such substituents, the 1,2,3-triols have been thoroughly characterized by Posternak[2]; however, the corresponding triamines and the aldiamines apparently are wholly unknown, and only one investigation[3] of the aminediols has been reported.

A suitable starting material for preparation of the aminediols appeared to be 1-ethoxy-2,3-epoxycyclohexane, whose preparation *via* the iodohydrin,[4] and also directly from 1-ethoxycyclohexene-2 by peracid treatment,[3] had been described. We found that a procedure using the chlorohydrin is somewhat more convenient, but the peracid method does give much better yields.

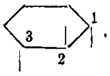
The reaction of the ethoxy-epoxide with ethanolic ammonia gave us an aminediol monoethyl ether[5] of m.p. 132–134°. Its N-*p*-nitrobenzoyl derivative melted at 201–203°. Cleavage of the aminediol ether with hydrobromic acid gave the aminediol as its hydrobromide, m.p. 167–168°. The aminediol was further characterized by conversion of the hydrobromide to the N-*p*-nitrobenzoyl derivative, which melted at 182–183°.



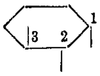
I



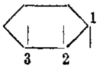
II



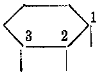
III
(1,3-*cis*)



IV
(1,2-*cis*)



V
(2,3-*cis*)



VI
(1,2,3-*cis*)

(Y = H, or H·HBr, or *p*-$COC_6H_4NO_2$)

For each of these four derivatives two structures (I or II) are possible, depending on whether the parent aminediol is 3-aminocyclohexanediol-1,2 or 2-aminocyclohexanediol-1,3. Structure I will result if the nucleophilic attack by $:NH_3$ on 1-ethoxy-2,3-epoxycyclohexane occurs at position 3, structure II if the attack is at position 2.

In order to determine the structure, periodic acid studies were carried out. The aminediol N-*p*-nitrobenzoyl derivative consumed nearly the theoretical amount of periodic acid for one –CHOHCHOH– grouping, thus supporting structure I.[6]

For each *structure* (I or II) four diastereomeric *configurations* (III, IV, V, VI) are possible.[7] Since oxirane ring opening generally occurs in the *trans* manner, the aminediol of structure I might have configuration III or IV but not V or VI. To decide between III and IV one must know not only the position of nucleophilic attack, but also the configuration of the ethoxy-epoxide used. The configuration of the epoxide must be either *d,l*-V or *d,l*-VI, since the cyclohexane–oxirane ring-fusion is necessarily *cis*.[8,8a]

Possible evidence on the configuration of the ethoxy-epoxide may be found in the work of Posternak,[2] who showed that it is hydrolyzed by water to give (after ether-cleavage by hydrobromic acid, which presumably causes no inversion) predominantly the *meso*-triol of configuration III.[9] Unfortunately, it is not known whether the presumed nucleophilic attack by $:\ddot{O}H_2$ on the oxide ring is at position 2, or at position 3. Hence the configurations of the ethoxy-epoxide and of our aminediol derivatives remain uncertain.

An earlier attempt to prepare an aminediol of structure II from the corresponding nitrodiol was

---

[1] For related publications see G. E. McCasland and Donald A. Smith, THIS JOURNAL, **73**, 5164 (1951), and references there cited.

[2] T. Posternak, *Helv. Chim. Acta*, **30**, 441 (1947).

[3] M. Mousseron, F. Winternitz and G. Combes, *Bull. soc. chim.*, [5] **14**, 79 (1947); M. Mousseron and R. Granger, *ibid.*, [5] **14**, 850 (1947); M. Mousseron, G. Manon and G. Combes, *ibid.*, [5] **16**, 396 (1949).

[4] L. Brunel, *Compt. rend.*, **150**, 986 (1910); *Ann. chim. phys.*, [8] **6**, 269 (1905).

[5] Mousseron, *et al.*,[3] reportedly obtained by the amination of this same ethoxy-epoxide an aminediol monoethyl ether of m.p. 110°, b.p. 148–150° (15 mm.), whose hydrochloride melted at 160° and contained 9.7% N (calcd. 7.2%). The free base reportedly reacted with nitrous acid to give 1-ethoxy-2-formylcyclopentane (semicarbazone m.p. 204–205°). Yields were not reported, and the compounds were not further characterized. The product of m.p. 110° could be an isomer, but is perhaps merely a less pure sample, of the compound of m.p. 134° now reported. In early 1947 Mousseron, *et al.*, assigned their product structure I, but later wavered between I and II. It should be noted that, according to current interpretations of the pinacolic rearrangement (*e.g.*, see G. E. McCasland, THIS JOURNAL, **73**, 2293 (1951)), both structures I and II might be expected to yield the above aldehyde.

[6] It is conceivable that a periodic acid solution of low *p*H might cause N → O acyl migration in a compound of structure –CHOHCH(NHCOR)CHOH–. This would produce a structure –CH(OCOR)-$CHNH_2$CHOH– scissionable by periodate. So far as we know, no one has found, or looked for, such an effect. However, since in any case the periodate oxidation of a 2-aminocyclanol is very slow at low *p*H[1], we regard it as improbable that the observed periodate uptake was due to acyl migration.

[7] For structure II, configurations IV and V become identical when both hydroxyl groups are free; therefore only three diastereomers would be predicted for such derivatives.

[8] The possible presence of both diastereomers in the ethoxy-epoxide as ordinarily prepared has not been entirely excluded.

[8a] FOOTNOTE ADDED IN PROOF.—Dr. J. A. McRae and Dr. R. Y. Moir of Queens University (Kingston), advise in a private communication that they have actually found two diastereomers in the ethoxy-epoxide prepared from the chlorohydrin, and will describe the separation and identification of these diastereomers in a forthcoming publication.

[9] A small proportion of the *d,l*-triol of configuration IV (= V) is simultaneously formed. The *meso*-triol of the all-*cis* configuration VI is obtained by hydrogenating pyrogallol.

abandoned when it was found that the yield of the nitrodiol from a condensation of pentanedial and nitromethane could not be raised above 3%.

Work on the trifunctional aminocyclanols is to be continued.

Experimental

All m.ps. are corrected. Microanalyses by Mr. R. Pyke.

d,l-**1-Ethoxy-2-chlorocyclohexanol-3**[10,11] (A).—Instead of using chlorine gas, aqueous hypochlorous acid was prepared by acidifying commercial 5 or 12% sodium hypochlorite solution (available at grocery stores). About 0.09 mole of the hypochlorous acid solution was added at 0° in portions to 0.055 mole of 1-ethoxycyclohexene-2.[12] After the last portion was added the mixture was stirred one hour longer at 0°, and the chlorohydrin was then extracted with benzene. The dried benzene extract was distilled *in vacuo* and the product collected at 110–117° (12 mm.). The crude product was redistilled, giving a 41% yield of colorless liquid, b.p. 98–105° (7.5 mm.), $n^{21}\mathrm{D}$ 1.4839 (reported[3] $n^{25}\mathrm{D}$ 1.4817, 1.4810).

(B).—The procedure was carried out with an N-chlorourea solution, according to the general procedure of Detoeuf,[13] giving the product in 35% yield.

d,l-**1-Ethoxy-2,3-epoxycyclohexane**[10,14] (A).—Treatment of the chlorohydrin with a dry ethereal suspension of powdered sodium hydroxide gave a 26% yield of colorless liquid, b.p. 74–77° (7 mm.). The procedure was like that used by Brunel[4] on the iodohydrin.

(B).—The chlorohydrin was treated with aqueous sodium hydroxide. The procedure was like that which had been used by Osterberg[15] on 2-chlorocyclohexanol. The yield was 23%.

(C).—Treatment of 1-ethoxycyclohexene-2[12] (b.p. 55–60° (12–15 mm.)) with perbenzoic acid by the procedure of Mousseron, *et al.*,[3] gave a 70% yield of the epoxide, b.p. 79–82° (15–16 mm.), $n^{25}\mathrm{D}$ 1.4530 (reported[3] 1.4493).

d,l-**3-Amino-1-ethoxycyclohexanol-2.**[16,17]—A solution of 2.0 g. of the ethoxy-epoxide in 25 ml. of ethanol (saturated at 25° with dry ammonia) was heated in a sealed tube for six hours at 120°. Ethanol and ammonia were then removed by vacuum distillation and the residue washed well with petroleum ether (60–70°). The residue was sublimed under vacuum and recrystallized thrice from benzene–petroleum ether (1:9). The yield of colorless crystals, m.p. 132–134°, was 0.35 g. (16%).

Anal. Calcd. for $C_8H_{17}NO_2$: neut. equiv., 159. Found: neut. equiv., 158.

Variations of temperature or time did not improve the above yield. The aminediol was characterized by conversion to the derivatives below.

d,l-**3-*p*-Nitrobenzoylamino-1-ethoxycyclohexanol-2.**[16,17]—An acylation procedure similar to that of Leffler and Adams[18] gave a 60% yield of colorless needles, which after recrystallization from 20% ethanol melted at 201–203° (dec.).

Anal. Calcd. for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.54; H, 6.80; N, 8.99.

d,l-**3-Aminocyclohexanediol-1,2 Hydrobromide.**[16,17]—A 5.0-g. portion of the aminediol monoethyl ether was boiled under reflux for 90 minutes with 23 ml. of 47% aqueous hydrobromic acid. The solution was vacuum distilled to dryness. Water (100 ml.) was added, and the resulting solution again distilled to dryness. Finally, 250 ml. of water was added, the mixture refluxed for two hours, and again distilled to dryness.

The gummy residue was taken up in a minimum volume of boiling ethanol–benzene (2:3), and pure benzene was added until crystals separated. The crude product (m.p. 150–170°) was recrystallized in a similar manner, giving 2.67 g. (40%) of crystalline hydrobromide, m.p. 167–168°.

Anal. Calcd. for $C_6H_{14}BrNO_2$: C, 33.97; H, 6.65; N, 6.61. Found: C, 33.78; H, 7.03; N, 6.72.

d,l-**3-*p*-Nitrobenzoylaminocyclohexanediol-1,2.**[16,17]—Acylation of the neutralized hydrobromide with *p*-nitrobenzoyl chloride as above gave a 49% yield of colorless plates. After two recrystallizations from 20% ethanol the compound melted at 182–183° (dec.) when heated rapidly.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 10.00. Found: C, 55.46; H, 6.30; N, 9.50.

Oxidation of the Nitrobenzoylaminocyclohexanediol with Periodic Acid.—An 18.3-mg. sample of the *p*-nitrobenzoylaminocyclohexanediol was treated with 2.72 ml. of 18.4 millimolar aqueous paraperiodic acid at 25° with stirring. Iodometric titrations with sodium arsenite revealed that 0.95–0.97 mole of periodic acid per mole of acylaminediol had been consumed within 20–30 minutes.

2-Nitrocyclohexanediol-1,3.[16]—A 1.5-g. portion of pentanedial[19] and equimolar quantities of nitromethane and 10% aqueous sodium hydroxide solution were allowed to react. The reaction mixture was neutralized, vacuum distilled, and the product obtained from the residue by ether extraction. The best yield obtained was only 3%. The product gave negative Schiff and Fehling tests for free aldehyde groups, and melted at 139–142°; analysis indicated it is not entirely pure. The configuration is not known; three diastereomers are possible.

Anal. Calcd. for $C_6H_{11}NO_4$: C, 44.72; H, 6.83; N, 8.70. Found: C, 44.76; H, 7.11; N, 9.76.

---

[10] The homogeneity of this product is not well established.

[11] Of four possible diastereomeric configurations for this product, only the configurations (1,2-*cis*) and (1,3-*cis*) are probable. On the basis of the limited evidence now available we consider the configuration (1,2-*cis*) more probable.

[12] F. Hoffman and P. Damm, *Chem. Zentr.*, **97**, I, 2342 (1926).

[13] A. Detoeuf, *Bull. soc. chim.*, [4] **31**, 102 (1922); J. A. McRae, E. H. Charlesworth and D. S. Alexander, *Can. J. Research*, **21B**, 5 (1943).

[14] Of four possible diastereomeric configurations for this product, only the configurations (2,3-*cis*) and (1,2,3-*cis*) are probable. On the basis of the limited evidence now available we consider the configuration (2,3-*cis*) more probable.

[15] A. E. Osterberg, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 185.

[16] It is believed that this product is homogeneous and consists of a single pure diastereomer.

[17] Of four possible diastereomeric configurations for this product, only the configurations (1,3-*cis*) and (1,2-*cis*) are probable. On the basis of the limited evidence now available we consider the configuration (1,3-*cis*) more probable.

[18] M. T. Leffler and R. Adams, THIS JOURNAL, **59**, 2256 (1937).

[19] The dial was prepared from cyclopentene ozonide (*ibid.*, **65**, 2183 (1943); *Ber.*, **41**, 1705 (1908); or, better, by the cleavage of cyclopentanediol-1,2 with lead tetraacetate (*Ann.*, **518**, 26 (1935)).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF TORONTO
TORONTO, CANADA

Grignard Preparation of Fluorene-2-Carboxylic Acid[1]

BY D. C. MORRISON

RECEIVED NOVEMBER 16, 1951

In connection with work on incorporation of isotopic elements into the fluorene molecule, the preparation of a Grignard reagent from 2-bromofluorene was studied. Under certain conditions this was found to be successful and carbonation of the resulting reagent solution furnished the 2-carboxylic acid. The difficulty of forcing a reaction between magnesium and bromo derivatives of polynuclear aromatic hydrocarbons is well recognized. Miller and Bachman[2] did not observe formation of the Grignard reagent from 2-bromofluorene by use of conventional techniques. In the present work, this reagent was obtained in about 20% yields by the reaction of a mixture of 2-bromofluorene and ethyl bromide with magnesium.

This entrainment reaction was carried out at ether reflux temperature and under these conditions

---

[1] The work described in this paper was sponsored by the Atomic Energy Commission. It was supported in part by a grant from the Henry, Laura and Irene B. Dernham Fund of the American Cancer Society and the Christine Breon Fund.

[2] H. F. Miller and G. B. Bachman, THIS JOURNAL, **57**, 766 (1935).