N-Substituted Cyclopropylamines

By M. FREIFELDER and BRUCE W. HORROM

A NEED IN this laboratory for some *N*-substituted cyclopropylamines of type A prompted an in-

$$\Delta NHCH\overset{\frown}{(CH_2)_n} \quad n = 2 \text{ to } 6$$

A

vestigation of their synthesis. All but dicyclopropylamine were readily obtained by reductive alkylation of cyclopropylamine with the corresponding cyclic ketone in the presence of platinum oxide. Since cyclopropanone was not available, acetone was substituted to give the structurally related *N*-isopropylcyclopropylamine.

Attempts to isolate and distill *N*-cycloheptylidenecyclopropylamine gave a mixture of products of constantly rising boiling points and changing refractive indices. The inability of the product of condensation of amine and ketones to withstand heating in the course of solvent removal discouraged any further effort to isolate and characterize the other intermediate Schiff bases. Each intermediate, however, was identified in solution by means of its infrared spectrum.[1] The amine and ketone (excluding acetone) were mixed in thiophene free benzene. Water separated from the mixture upon standing and anhydrous magnesium sulfate was added. After removal of drying agent, a sample of the solution showed the presence of C=N function by the characteristic band at 6.1 μ. The remainder of the benzene solution was then hydrogenated in the presence of platinum oxide. In the reaction with acetone, equimolar amounts of amine and acetone were mixed, allowed to stand, and then hydrogenated in the presence of platinum oxide.

EXPERIMENTAL

The following is characteristic of the preparation of the *N*-cycloalkylcyclopropylamines listed in Table I.

N-Cyclobutylcyclopropylamine.—A 10-Gm. (0.1428 mole) quantity of cyclobutanone[2] was added to 8.14 Gm. (0.1428 mole) of cyclopropylamine[2] in 50 ml. of anhydrous thiophene free benzene and allowed to stand for 1 hour. Slight warming occurred, and water began to separate. Then 10.0 Gm. of anhydrous magnesium sulfate was added and the mixture allowed to stand for an additional hour. The drying agent was filtered and washed with 25–50 ml. of thiophene free benzene. The filtrate was hydrogenated under 2 atm. pressure in the presence of 0.3 Gm. of platinum oxide. When the uptake of hydrogen was complete (1.5 hours), the benzene solution was filtered from the catalyst. The solvent was distilled off and the residue fractionated. The benzene distillate contained a considerable amount of I. Additional yield as hydrochloride salt was obtained by treating the distillate with alcoholic hydrogen chloride, concentrating the solution to dryness, and recrystallizing the salt from hot acetone.

TABLE I.— *N*-CYCLOALKYLCYCLOPROPYL AMINES PREPARED

ΔNHR

	R	Yield, %	Constants, B.p., °C.	mm.	$n^{25}D$	Hydrochloride m.p., °C.	Formula	Analyses[b,c] C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
I	Cyclobutyl	[a]	130	753	1.4509	...	$C_7H_{13}N$	75.63	74.42	11.78	11.94	12.59	12.48
II	Cyclopentyl	84.3	90–94	68	1.4621	158–160	$C_7H_{14}ClN$	56.93	57.06	9.55	9.57	9.48	9.64
							$C_8H_{15}N$	76.73	77.04	12.08	11.83	11.19	11.09
III	Cyclohexyl	94.1	114–118	34–35	1.4774	169–171	$C_8H_{16}ClN$	59.42	59.54	9.97	9.95	8.66	8.70
							$C_9H_{17}N$	77.63	77.64	12.31	12.51	10.07	10.06
IV	Cycloheptyl	78.4	100–104	40	1.4683	147	$C_9H_{18}ClN$	61.52	61.45	10.32	10.43	7.97	7.99
							$C_{10}H_{19}N$	...	...	...	...	...	...
V	Isopropyl	64.6	98–100	755	1.4136	153–154	$C_{10}H_{20}ClN$	63.30	63.17	10.62	10.94	7.38	7.35
		63.0	...	...	...	163–165	$C_6H_{13}N$	...	...	...	...	...	...
							$C_6H_{14}ClN$	53.12	52.97	10.40	10.66	10.33	10.13

[a] The yield consisted of 46% of material as base and 30% as hydrochloride salt. [b] Rapid absorption of carbon dioxide by the bases made satisfactory analytical values for carbon and hydrogen difficult to obtain. In some instances when the analyses were carried out immediately after distillation good values resulted. In others it was necessary to characterize the compound by means of its hydrochloride salt. [c] Microanalyses carried out by Mr. O. Kolsto and his group in this laboratory.

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[1] Work done in this laboratory by Mr. A. Kammer and Mr. W. Washburn.

[2] The cyclic ketones and cyclopropylamine are available from the Aldrich Chemical Co., Milwaukee, Wis.

In the preparation of the higher homologs, a slight excess of cyclopropylamine was used. Distillation of the resultant products of reduction was uncomplicated.

N-Isopropylcyclopropylamine.—Cyclopropylamine (28.5 Gm., 0.5 mole) and 31.8 Gm. (0.5 mole) of acetone were mixed and allowed to stand for 1 hour, then hydrogenated under 2–3 atm. pressure in the presence of 1.0 Gm. of platinum oxide. After uptake of hydrogen was complete (6 hours), the mixture was allowed to stand until the catalyst settled. The solution was decanted from the catalyst in a nitrogen atmosphere. *Caution!* In air the catalyst may ignite the vapors of the low boiling liquid. The base, which contained some water, was treated with solid potassium hydroxide. It was separated and distilled. A hydrochloride salt was prepared for identification.

In another experiment the reduction was carried out in alcohol. The filtered solution was treated with an equivalent of alcoholic hydrogen chloride and the salt obtained after concentration.

Synthesis of the Diuretic 8-Chloroalloxazine-5,10-dioxide

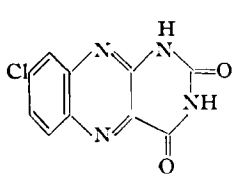
By H. G. PETERING and G. J. VAN GIESSEN

The synthesis of 8-chloroalloxazine-5,10-dioxide, a new diuretic, is described. It has advantages over 8-chloroalloxazine in that it is readily solubilized in aqueous media containing arginine or tris-buffer (THAM).

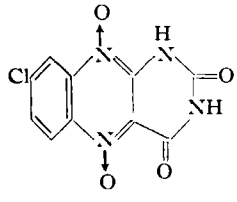
RECENTLY Petering and Van Giessen (1) reported the synthesis of a new diuretic, 8-chloroalloxazine (I) and of several related alloxazines and quinoxalines. In extending the study of the relationship of diuretic activity to chemical structure in this series of compounds, 8-chloroalloxazine-5,10-dioxide (II) has now been prepared. It was found by B. E. Graham in this laboratory (2) to be the only one with diuretic activity comparable to I. Moreover, II can be readily solubilized in water by the addition of arginine or tris-hydroxymethylaminomethane (tris or THAM). Because of the biological potentialities of this compound, its synthesis is presented here.

EXPERIMENTAL

Synthesis.—8-Chloroalloxazine (2.5 Gm.) was suspended in a mixture of 100 ml. 88% formic acid and 10 ml. 30% hydrogen peroxide. The mixture was warmed to 65° on a water bath. The heat was removed as the exothermic reaction began. The reaction temperature was allowed to rise to 95°. (An ice bath was kept on hand to permit rapid cooling in case the reaction became violent.) A rapid evolution of gas occurred when the temperature reached 75–80°, all of the insoluble material went into solution, and the color deepened from pale yellow to orange. Shortly thereafter, crystals of II began to form. After the evolution of gas had ceased, the mixture was allowed to cool to room temperature and was refrigerated at 5° for 48 hours.



8-Chloroalloxazine (I)



8-Chloroalloxazine-5,10-dioxide (II)

The orange crystals were collected and washed with small amounts of cold water, ethanol, and acetone. The yield of air-dried product was 2.4 Gm. or 85% of theory, m.p. 285–292°.

When glacial acetic acid was used as the solvent, II was obtained in 81% yield, m.p. 293–295°.

Recrystallization of II from methylcellosolve raised the melting point to 297–298° (Product A). Recrystallization from a mixture of 88% formic acid containing 10% of hydrogen peroxide (30%) gave 80% yield of II, m.p. 300–301° (Product B). Recrystallization can also be effected from 95% ethanol.

Anal.—Calcd. for $C_{10}H_5ClN_4O_4$: C, 42.8; H, 1.8; Cl, 12.6; N, 20.0; O, 22.8. Found: Product A—C, 43.4; H, 2.4; Cl, 11.7; N, 19.7; O, 23.8. Product B—C, 43.6; H, 1.2; Cl, 12.0; N, 19.2; O, 20.9.

Infrared Spectrum.—The I.R. spectral analyses of Products A and B mentioned above were identical and showed the required bands for the structure proposed for II. N—H, 3140 (sh) and 3050 $cm.^{-1}$; C = 0, 1715–1708 $cm.^{-1}$; C = C/C N, 1608, 1580–1572, 1500(sh), 1480(sh) $cm.^{-1}$; N→0, 1340, 1246, and 1235 (sh) $cm.^{-1}$.

Ultraviolet Spectrum.—The U.V. spectral analyses showed no evidence of the presence of I, but distinctive bands characteristic of II. The ϵ values are as follows: 281.5 mμ, 62,600; 346 mμ, 6150; 459 mμ, 9100.

Chromatography on circular disk paper using as solvent *n*-butanol 6, pyridine 4, water 3 (v/v/v), showed one ultraviolet fluorescing band at R_f 0.48, with a very faint trace of fluorescence at 0.66 which was not identified. The R_f of I in this solvent is 0.81.

8-Chloroalloxazine-5,10-dioxide is soluble to the extent of 12.5 mg. per 100 ml. of water and 6 mg. per 100 ml. of physiological saline. This solubility is raised to 830 mg. per 100 ml. of 0.1 *M* arginine and to 625 mg. per 100 ml. of 0.1 *M* tris-buffer (THAM), with resulting pH values of 7.0 in each case. The dioxide is also solubilized by sodium and potassium bicarbonate.

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