[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF NEW YORK, NEW YORK STATE COLLEGE FOR TEACHERS]

Convenient Syntheses of 1,2,3,4-Tetrahydroquinoxalines

RICHARD F. SMITH, WILLIAM J. REBEL, AND THAISA N. BEACH

Received September 19, 1958

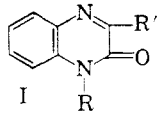
New and convenient syntheses of 1,2,3,4-tetrahydroquinoxaline (THQ) derivatives have been developed. Lithium aluminum hydride reduction of the readily available 2-keto-THQ (II) afforded THQ. Alkylation of II with simple alkyl halides yielded 1-alkyl-3-keto-THQ derivatives (III) which underwent reduction with lithium aluminum hydride to give the corresponding 1-alkyl-THQ (IV) in excellent yields (Method *A*). Sodium borohydride reduction of the methyl *p*-toluenesulfonate and ethyl iodide quaternary salts of quinoxaline afforded the corresponding IV derivatives (Method *B*). Lithium aluminum hydride reduction of 6-chloroquinoxaline yielded 6-chloro-THQ.

The pharmacological activity of piperazine derivatives is well documented and it seemed worthwhile to prepare the structurally similar 1,2,3,4-tetrahydroquinoxaline (THQ) derivatives for evaluation.

The difficulties encountered in the preparation of simple 1-alkyl-THQ derivatives have been established by Cavagnol and Wiselogle[1] who attempted monoalkylation and monoacylation of THQ with a variety of reagents using different solvents and temperatures ranging from −70° to 300°. In all cases the only products isolated were starting material or the disubstituted THQ. It was later found[2] that monoacylation could be accomplished in yields up to 70% by operating at *p*H 6–7.

Cavagnol and Wiselogle[1] found that monophenylsulfonation could be accomplished in good yields and were able to synthesize a variety of 1-alkyl-THQ derivatives (IV) by the sequence: Quinoxaline→THQ→1-phenylsulfonyl-THQ→1-alkyl-4-phenylsulfonyl-THQ→IV. The over-all yields (based on quinoxaline) were 42–58%.

The synthesis of a few 1-substituted THQ compounds has recently been accomplished[3] by the lithium aluminum hydride reduction of 1-alkyl-2-keto-1,2-dihydroquinoxalines (I) which are prepared by the reaction of *N*-substituted *o*-phenylenediamines with α-ketoacids. A few complex 1-substituted THQ derivatives have been prepared by catalytic reduction of quinoxaline quaternary salts.[3]



I

Two new and convenient syntheses have been developed for simple IV type compounds.

Method *A* utilizes as starting material the readily available 2-keto-THQ (II). Compound II is prepared[4] by simply heating *o*-phenylenediamine and chloroacetic acid in dilute aqueous ammonia. Alkylation of II with ethyl-, *n*-propyl- and *n*-butyl iodides and benzyl chloride in ethanolic solution gave moderate to good yields (Table I) of the 1-alkyl-3-keto-THQ (III). All of the III compounds possessed wide melting ranges and were purified with great difficulty.[5] However, lithium aluminum hydride reduction of the crude III type compounds gave excellent yields of IV. The IV compounds were all characterized by their neutral equivalents and conversion to the known benzoyl and phenylsulfonyl derivatives.[1]

Lithium aluminum hydride reduction of II furnished THQ in 65% yield.

Method *B* utilizes the sodium borohydride reduction[6] of quinoxaline quaternary salts (V) to give the IV derivatives. This method is not of as great general synthetic importance as method *A* since quaternization of quinoxaline with higher alkyl halides proceeds in poor yields.[7] However, this method is probably the best for preparation of the 1-methyl and 1-ethyl THQ derivatives (IVa and IVb). Thus, methyl quinoxalinium *p*-toluenesulfonate[8] (Va) was obtained in quantitative yield and subsequent reduction gave a 64% yield

(1) J. C. Cavagnol and F. Y. Wiselogle, *J. Am. Chem. Soc.*, **69**, 795 (1947).

(2) J. S. Morley, *J. Chem. Soc.*, 4002 (1952).

(3) J. Druey and A. Huni, *Helv. Chim. Acta*, **35**, 2301 (1952).

(4) W. H. Perkin, Jr., and G. C. Riley, *J. Chem. Soc.*, **123**, 2399 (1923).

(5) P. van Romburgh and W. B. Deys, *Proc. Acad. Sci. Amsterdam*, **34**, 1004 (1931). This reference cites the only recorded alkylation of II. Ethyl iodide and II were reacted without solvent in a sealed tube at 100° to give 1-ethyl-3-keto-THQ in unspecified yield, m.p. 98–99°. In experiments carried out by Mr. Robert Hyde in these laboratories, none of the 98–99° product could be isolated by the above method. The product isolated by our procedure (IIIb) had m.p. 112–114° and gave the correct analysis (Table I).

(6) For references on the borohydride reduction of other quaternary salts see: N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, Inc., New York, pp. 789–93.

(7) (a) Y. T. Pratt in *Heterocyclic Compounds*, R. C. Elderfield, ed., John Wiley and Sons, New York, 1957, Vol. 6, p. 472. (b) W. K. Easly and C. T. Bahner, *J. Am. Chem. Soc.*, **72**, 3803 (1950).

(8) C. T. Bahner, L. R. Barclay, G. Biggerstaff, D. L. Bilancio, G. W. Blanc, M. Close, M. M. Isenberg, and E. Pace, *J. Am. Chem. Soc.*, **75**, 4838 (1953).

TABLE I

1-ALKYL-1,2,3,4-TETRAHYDRO-3-KETOQUINOXALINES (III)

Formula	Crude Yield	m.p.°C.	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
IIIb, $C_{10}H_{12}N_2O$	60	112–114	68.15	6.87	15.90	68.45	6.99	15.86
IIIc, $C_{11}H_{14}N_2O$	51	97–99	69.44	7.42	14.73	69.63	7.60	14.55
IIId, $C_{12}H_{16}N_2O$	61	101–103	70.55	7.90	13.74	70.44	7.90	13.60
IIIe, $C_{15}H_{14}N_2O$	90	130[a]	75.60	5.92	11.76	75.27	6.20	11.59

[a] Prior softening.

TABLE II

1-ALKYL-1,2,3,4-TETRAHYDROQUINOXALINES

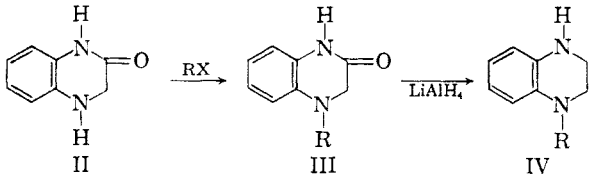
Formula	Method	Yield	B.P. °C.	Mm.	Neutral Equivalents Calcd.[a]	Found
IVa $C_9H_{12}N_2$	*B*	64	163–169	21	148	148
IVb $C_{10}H_{14}N_2$	*A*	80	170–173	21	162	162
IVb	*B*	72	168–173	21		
IVc $C_{11}H_{16}N_2$	*A*	91	176–179	20	176	176
IVd $C_{12}H_{18}N_2$	*A*	76	187–191	21	190	191
IVe $C_{15}H_{16}N_2$	*A*	82	242–250	19	224	232

[a] The neutral equivalents were determined by titration with perchloric acid in acetic acid.

of IVa. The ethyl iodide[9] salt (Vb) was obtained in 76% yield and afforded 72% of IVb on reduction.

The 76% yield of Vb could be achieved only if the quaternization was carried out in refluxing acetonitrile. Attempted quaternization of quinoxaline with *n*-propyl iodide, *n*-butyl iodide, and benzyl chloride in refluxing acetonitrile gave only small amounts of crystalline material accompanied by extensive decomposition.

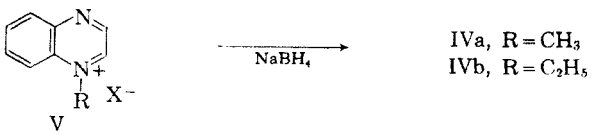
Method *A*



II III IV

b. R = Et
c. R = *n*-C_3H_7
d. R = *n*-C_4H_9
e. R = benzyl

Method *B*



V

IVa, R = CH_3
IVb, R = C_2H_5

a. R = Me; X = $C_7H_7SO_2^-$
b. R = Et; X = I^-

(9) O. Hinsberg, *Ann.*, **292**, 245 (1896).

Although the over-all yields of the type IV compounds prepared by the new procedures do not represent any great improvement in over-all yield (based on *o*-phenylenediamine), the metal hydride syntheses are certainly less time-consuming than the earlier method of Cavagnol and Wiselogle[1] and appear to be the method of choice for moderate scale preparation of simple monoalkyl-THQ compounds.

The methyl compound (IVa) was also converted to the urea derivative, the phenylurea derivative, and 1,1,4-trimethyl-1,2,3,4-tetrahydroquinoxalinium iodide.

We have also prepared 6-chloro-THQ in 65% yield by the lithium aluminum hydride reduction[10] of 6-chloroquinoxaline. Cavagnol and Wiselogle[1] obtained only trace amounts of 6-chloro-THQ by catalytic reduction.

It is planned to prepare several new derivatives of the IV compounds which will be substituted with groups that may confer biological activity. Several of the compounds described in this paper have been submitted for pharmacological evaluation to Dr. Carl Pfeiffer, Division of Basic Health Sciences, Emory University, Atlanta, Ga.

EXPERIMENTAL

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Analyses are by Mr. K. D. Fleischer and his staff of the Microanalytical Laboratory of Sterling-Winthrop Research Institute, Rensselaer, N. Y.

1,2,3,4-Tetrahydro-2-ketoquinoxaline (II). This compound was prepared by the method of Perkin and Riley.[4] When run on a 2.2 mole scale the yield of unpurified product was 65%. The product was obtained as tan crystals, m.p. 130–135° after drying at 100°. The crude material was used in all experiments.

1,2,3,4-Tetrahydroquinoxaline. A suspension of 8.0 g. of lithium aluminum hydride in 500 cc. of dry ether was prepared in a 1 l. flask equipped with an air stirrer and efficient condenser with a calcium chloride tube attached. To this suspension was added, with stirring, 14.3 g. (0.097 m.) of II

(10) F. Bohlmann, *Ber.*, **85**, 390 (1952), reported the reduction of quinoxaline to THQ with lithium aluminum hydride.

in small portions. After the original reaction had subsided the contents were stirred and refluxed for 4 hr. The reaction mixture was treated cautiously with the minimum amount of water to effect decomposition and the inorganic material was filtered and washed with ether. Evaporation of the ether solution and recrystallization from benzene–petroleum ether gave 8.4 g. (64.6%) of white crystals, m.p. 94–97°. The reported[1] m.p. is 98.5–99°.

The *dibenzoyl derivative* melted at 205–207°. The reported[1] m.p. is 206–207°.

General method for alkylation of II. A suspension of 0.2 mole of anhydrous sodium carbonate, 0.1 mole of II, 0.11 mole of the alkyl iodide (or benzyl chloride) and 75–100 cc. of 95% ethanol was stirred and refluxed overnight. The reaction mixture was poured into 1 l. of water and the resultant oils crystallized rapidly. The brown solids were washed with water and dried in a vacuum desiccator (calcium chloride) overnight. The dried solids usually had very wide melting ranges but were used directly for lithium aluminum hydride reduction. Purification of small samples for analysis was accompanied by large losses of material, and several recrystallizations were usually needed to obtain the melting points recorded in Table I for the 1-alkyl-1,2,3,4-tetrahydro-3-ketoquinoxalines (III). Attempted alkylation with methyl iodide gave a very poor yield of solid. Compound IIIb was recrystallized from benzene-hexane, the others from ethanol. Compound IIIc was obtained as white crystals, the others formed yellow crystals.

1-Alkyl-1,2,3,4-tetrahydroquinoxalines by method A. The crude III was added in small portions to a suspension of a large excess of lithium aluminum hydride (about a 1:3 hydride to III weight ratio) suspended in dry ether and contained in a flask equipped with an efficient condenser (calcium chloride tube). After the initial reaction had subsided the reaction mixture was refluxed 1 hr., then treated dropwise with the minimum amount of water required for decomposition. The inorganic material was filtered, washed with benzene, and the combined solutions evaporated at reduced pressure. The resultant oils were immediately distilled at reduced pressure through a Claisen head. The products were yellow oils which darkened rapidly.

Methyl quinoxalinium p-toluenesulfonate (Va). A mixture of distilled quinoxaline (10 g.) and 20 cc. of methyl *p*-toluenesulfonate was allowed to remain at room temperature for four days. The resultant solid was broken up under dry ether, filtered, and dried. A quantitative yield of light purple solid, m.p. 143–147° was obtained and used for subsequent reduction. Recrystallization from ethanol-ether gave white crystals, m.p. 150–152°. The reported[8] melting point is 150°. The salt was quite hygroscopic.

1,2,3,4-Tetrahydro-1-methylquinoxaline (IVa) *by method B.* Crude Va (98 g.) was dissolved in 150 cc. of water and extracted once with ether to remove non-ionic impurities. The water solution was added dropwise with stirring over 0.5 hr. to a solution of 35 g. of sodium borohydride in 1 l. of water and cooled by a cold water bath. After 10 min. of additional stirring, the product was separated by three extractions with benzene. The combined extracts were stirred with 10 g. of charcoal, filtered, and evaporated immediately at reduced pressure. Distillation through a Claisen head gave 31 g. (64.1%) of a yellow oil, b.p. 163–169° (21 mm.).

Initially, considerable decomposition of product was observed when the reduction of the methiodide was carried out in methanol-water and the extracts dried over magnesium sulfate prior to distillation.

Ethyl quinoxalinium iodide (Vb). Reaction of quinoxaline and ethyl iodide without solvent at room temperature and at 50° gave very poor yields. The following procedure gave the best results. A solution of quinoxaline (10 g.), ethyl iodide (20 cc.), and dry acetonitrile (50 cc.) were refluxed overnight. The red crystals were filtered and a second crop obtained by dilution with ether. The yield was 16.0 g. (76%), m.p. 141–143° (dec.). The reported[9] m.p. is 146° (dec.).

1-Ethyl-1,2,3,4-tetrahydroquinoxaline (IVb) *by method B.* The reduction of Vb was carried out as with Va except the solid ethiodide was added in small portions to the sodium borohydride solution. The product was separated with ether and distilled immediately.

Characterization of the 1-alkyl-1,2,3,4-tetrahydroquinoxalines. In addition to the neutral equivalents reported in Table II, all of the compounds were characterized by conversion to the benzoyl and phenylsulfonyl derivatives. Good agreement with recorded[1] melting points was obtained in all cases and the yields of pure derivatives were usually greater than 90%. The picrate of IVa also had the correct melting point.[1]

1,1,4-Trimethyl-1,2,3,4-tetrahydroquinoxalinium iodide. This compound was prepared by refluxing a mixture of 5 g. IVa, 12 cc. methyl iodide, 3.72 g. of sodium carbonate, and 30 cc. of absolute ethanol for 3.5 hr. The insoluble material was extracted with boiling methanol and the combined solutions were diluted with ether. The resultant white solid was recrystallized from absolute ethanol to give 2.8 g. of white crystals, m.p. 215–216°.

Anal. Calcd. for $C_{11}H_{11}IN_2$: C, 43.43; H, 5.63; I, 41.72. Found: C, 43.63; H, 5.86; I, 42.12.

1,2,3,4-Tetrahydro-1-methyl-4-phenylcarbamylquinoxaline. This compound was prepared by treating a solution of 2.9 g. IVa in 20 cc. of petroleum ether with 3.0 cc. of phenyl isocyanate. Recrystallization of the resultant solid gave 2.2 g. of white needles, m.p. 129–130°.

Anal. Calcd. for $C_{16}H_{17}N_3O$: C, 71.88; H, 6.41; N, 15.72. Found: C, 71.72; H, 6.48; N, 15.46.

1-Carbamyl-4-methyl-1,2,3,4-tetrahydroquinoxaline. This compound was prepared by treating a solution of 3 g. of IVa in 15 cc. of acetic acid and 30 cc. of water with a solution of 6 g. of potassium cyanate in 20 cc. of water. After warming on the steam bath for 5 min. and cooling the product separated. Recrystallization from aqueous ethanol gave 1.9 g. of white crystals, m.p. 124–125°.

Anal. Calcd. for $C_{10}H_{13}N_3O$: C, 62.81; H, 6.85; N, 21.98. Found: C, 63.12; H, 6.85; N, 21.83.

6-Chloro-1,2,3,4-tetrahydroquinoxaline. To a suspension of 5 g. of lithium aluminum hydride in 750 ml. of dry ether was added slowly with stirring 20 g. of 6-chloroquinoxaline[1] in 500 ml. of dry ether. After the initial reaction had subsided, the mixture was stirred and refluxed for 6 hr. Water (15 cc.) was added dropwise to the stirred solution and the insoluble material filtered and washed with benzene. The combined solutions were evaporated to give a white solid which was recrystallized from benzene–petroleum ether to give 13.4 g. (65.5%) of white crystals, m.p. 112–114°. The reported[1] m.p. is 113–114°.

The *dibenzoyl derivative* melted at 168–169°. The reported[1] m.p. is 168.5–169°.

Acknowledgment. The senior author wishes to express his thanks to Dean O. E. Lanford, President E. R. Collins, and Dr. D. V. Tieszen whose combined efforts made possible a special summer stipend and financial support of the work. Thanks are also due the Sterling-Winthrop Research Institute for microanalyses and use of library facilities.

ALBANY, N. Y.