[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

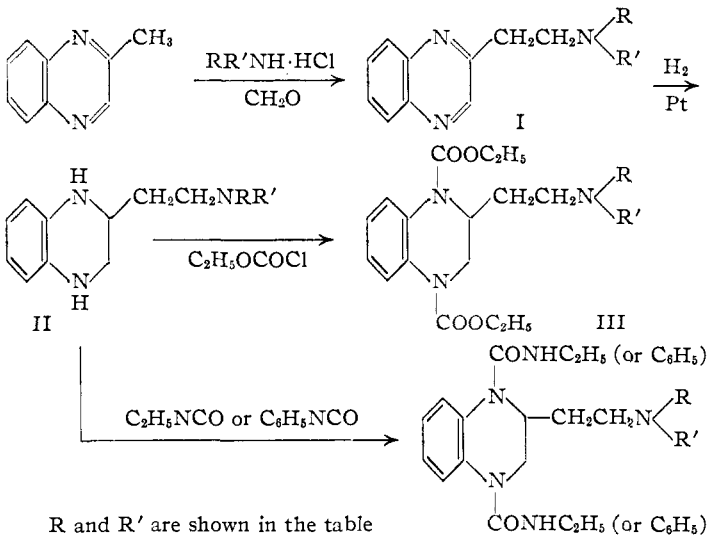
Pyrazine, Quinoxaline and Tetrahydroquinoxaline Derivatives

BY PAUL F. WILEY

RECEIVED APRIL 16, 1954

A number of pyrazines, quinoxalines and tetrahydroquinoxalines have been synthesized from 2-methylpyrazine and 2-methylquinoxaline *via* the Mannich reaction.

A number of pyrazine, quinoxaline and tetrahydroquinoxaline derivatives have been synthesized in a search for compounds which would be effective in human helminthic diseases. The new compounds prepared in this work except 2-diethylaminoethylpyrazine are listed in Table I. The method of synthesis for all except 2-diethylaminoethylpyrazine and 2-(2-carbethoxyethylaminoethyl)-quinoxaline is shown in the equation



R and R' are shown in the table

The reaction of 2-methylpyrazine with formalin and diethylamine hydrochloride gave 2-diethylaminoethylpyrazine. This compound was not obtained pure but was converted to its picrate and analyzed as such. 2-(2-Carbethoxyethylaminoethyl)-quinoxaline was synthesized by the reaction of ethyl chloroformate with 2-(2-ethylaminoethyl)-quinoxaline which was obtained by a Mannich reaction from 2-methylquinoxaline.

None of these compounds had appreciable antihelminthic activity.

Acknowledgment.—I wish to thank Mr. W. L. Brown, Mr. H. L. Hunter and Mr. W. J. Schenck for the microanalyses.

Experimental[1]

2-Methylpyrazine and 2-methylquinoxaline were prepared by the method of Jones, Kornfeld and McLaughlin.[2] 2-(2-Diethylaminoethyl)-quinoxaline has been reported by Wear and Hamilton[3] but was prepared by the following procedure for 2-(2-dialkylaminoethyl)-quinoxalines.

2-Diethylaminoethylpyrazine.—A mixture of 9.4 g. (0.1 mole) of 2-methylpyrazine, 11.0 g. (0.1 mole) of diethylamine hydrochloride and 8.4 g. (0.1 mole) of formalin was heated on the steam-bath for 15 hours. One hundred milliliters of ether was added, and the mixture was stirred vigorously while adding sufficient 50% sodium hydroxide solution to make the aqueous layer alkaline. Stirring was continued while the aqueous layer was saturated with solid sodium carbonate. The ether layer was removed and the aqueous layer was extracted with two more 100-ml. portions of ether. The combined ether extracts were dried with magnesium sulfate, filtered and concentrated. The residue was fractionated retaining the fraction boiling at 70–72° (0.6 mm.), yield 2.7 g. (15%). The product was refractionated retaining the fraction boiling at the same place; $n^{25}D$ 1.4943.

Anal. Calcd. for $C_{10}H_{17}N_3$: C, 67.03; H, 9.52; N, 23.46. Found: C, 65.35; H, 9.72; N, 23.20.

The picrate was prepared by adding about 0.5 g. to 20 ml. of alcohol saturated with picric acid and cooling. Three recrystallizations from alcohol gave a product melting at 103–105°.

Anal. Calcd. for $C_{16}H_{20}N_6O_7$: C, 47.06; H, 4.94; N, 20.59. Found: C, 47.08; H, 5.28; N, 20.87.

2-(2-Dialkylaminoethyl)-quinoxalines.—Forty-three and two-tenths grams (0.3 mole) of 2-methylquinoxaline, 0.3 mole of the appropriate dialkylamine hydrochloride and 25 ml. of formalin were mixed. In the cases using dimethylamine hydrochloride and diethylamine hydrochloride the reaction mixtures were heated on the steam-bath for 4–5 hours. In the cases using benzylethylamine hydrochloride and piperidine hydrochloride the reaction mixtures were stirred at 50–60° for five hours. Three hundred ml. of water was added and the solution was extracted with two 300-ml. portions of ether. The aqueous layer was made basic with 180 ml. of 10% sodium hydroxide solution and extracted with three 300-ml. portions of ether. The combined ether extracts were dried with magnesium sulfate. The drying agent was removed and the solvent was evaporated from the filtrate. The residual liquid was then fractionated.

2-(2-Carbethoxyethylaminoethyl)-quinoxaline (Id).—A mixture of 43.2 g. (0.3 mole) of 2-methylquinoxaline, 24.3 g. (0.3 mole) of ethylamine hydrochloride and 25 ml. of formalin was stirred at room temperature for 24 hours. The reaction mixture was then worked up as described in the preceding paragraph except that the product was not distilled.

The crude 2-(2-ethylaminoethyl)-quinoxaline was dissolved in 36 ml. of dry pyridine, and this solution was stirred while 30 g. (0.27 mole) of ethyl chloroformate in 60 ml. of dry benzene was added dropwise. The reaction mixture was maintained at 35–50° by moderate cooling. Stirring was continued until no more heat was evolved. Two hundred and twenty-five milliliters of water was added, and the mixture was neutralized by saturation with solid sodium bicarbonate. This was followed by extraction with four 100-ml. portions of benzene. The combined benzene extracts were concentrated by evaporation under reduced pressure. Fractionation of the residual black oil gave 3.9 g. (4.7%) of a light yellow oil boiling at 146–149° (0.2 mm.). Two more fractionations gave the pure product.

2-(2-Dialkylaminoethyl)-1,2,3,4-tetrahydroquinoxalines (IIa, IIb, IIc).—A solution of 0.1 mole of 2-(2-dialkylaminoethyl)-quinoxaline in 200 ml. of alcohol containing 0.2 g. of platinum oxide was shaken under hydrogen at an initial pressure of 50 lb. per sq. in. and at room temperature until hydrogen uptake ceased. The reaction mixture was fil-

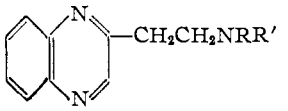
(1) The boiling points and melting points are uncorrected.

(2) R. G. Jones, E. C. Kornfeld and K. C. McLaughlin, THIS JOURNAL, **72**, 3539 (1950).

(3) R. L. Wear and C. S. Hamilton, *ibid.*, **72**, 2893 (1950).

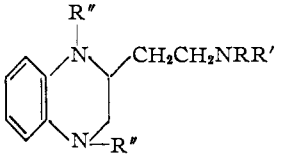
TABLE I

SECTION A



No.	Substituents R	R′	M.p. or b.p., °C.	Mm.	$n^{25}D$	Yield, %	Empirical formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found
Ia	CH_3	CH_3	109	0.6	1.5806	20.2	$C_{12}H_{15}N_3$	71.64	71.66	7.47	7.37	20.89	20.67
Ib	$C_6H_5CH_2$	C_2H_5	153–155	.15	1.5998	28.8	$C_{19}H_{21}N_3$	78.35	78.02	7.26	7.10	14.42	14.06
Ic	$(CH_2)_5N$		118	.15	1.5869	23.9	$C_{15}H_{19}N_3$	74.69	74.40	7.88	8.19	17.43	17.59
Id	C_2H_5	C_2H_5COO	140	.15	1.5618		$C_{15}H_{19}N_3O_2$	65.93	65.60	6.97	7.24	15.38	15.47

SECTION B



	R	R′	R″	M.p. or b.p., °C.	Mm.								
IIa[a]	CH_3	CH_3	H	120–124	0.2	74	$C_{12}H_{19}N_3$	70.24	70.53	9.37	9.21	20.49	20.16
IIb	C_2H_5	C_2H_5	H	140–142	.2	85	$C_{14}H_{23}N_3$	72.10	71.79	9.88	9.90	18.03	17.85
IIc[b]	$C_6H_5CH_2$	C_2H_5	H	178–185	.2	28	$C_{19}H_{25}N_3$	77.29	77.02	8.48	8.51	14.24	14.07
IIIa[c]	CH_3	CH_3	C_2H_5OCO	173	.7	81	$C_{18}H_{27}N_3O_4$	61.88	61.79	7.74	7.74	12.03	11.58
IIIb	C_2H_5	C_2H_5	C_2H_5OCO	160–164	.2	40	$C_{20}H_{31}N_3O_4$	63.64	63.32	8.28	8.38	11.12	11.29
IVa	CH_3	CH_3	C_2H_5NHCO	127–129[d]		49.6	$C_{18}H_{29}N_5O_2$	62.24	62.10	8.37	8.21	20.17	19.87
IVb	C_2H_5	C_2H_5	C_2H_5NHCO	138–140[d]		51.5	$C_{20}H_{33}N_5O_2$	64.97	65.04	8.88	8.97	18.64	18.59
IVc	CH_3	CH_3	C_6H_5NHCO	191–192[d]		47.7	$C_{26}H_{29}N_5O_2$	70.42	70.45	6.58	6.84	15.76	15.93
IVd	C_2H_5	C_2H_5	C_6H_5NHCO	148–150[d]		25.6	$C_{28}H_{33}N_5O_2$	71.31	71.31	7.06	7.00	14.83	14.72

[a] $n^{25}D$ 1.5750. [b] $n^{25}D$ 1.5943. [c] $n^{25}D$ 1.5322. [d] Melting points.

tered, and the filtrate was concentrated by evaporation under reduced pressure on the steam-bath. The residual oil was fractionated.

1,4-Dicarbethoxy-2-(2-dialkylaminoethyl)-1,2,3,4-tetrahydroquinoxalines (IIIa, IIIb).—A solution of 0.1 mole of 2-(2-dialkylaminoethyl)-1,2,3,4-tetrahydroquinoxaline in 50 ml. of dry pyridine was stirred while a solution of 23.8 g. (0.22 mole) of ethyl chloroformate in 70 ml. of dry benzene was added dropwise. The reaction mixture was cooled occasionally in order to keep the temperature at about 50°. After the addition of reactants was complete the reaction mixture was stirred at room temperature for two hours. Three hundred milliliters of water was added, and the mixture was neutralized with solid sodium bicarbonate. The organic layer was removed, and the aqueous layer was extracted with two 300-ml. portions of benzene. The extracts were combined with the organic layer, and the solvent was removed by evaporation under reduced pressure on the steam bath. The liquid residue was fractionated under reduced pressure.

1,4-Bis-(aryl- or alkylcarbamyl)-2-(2-diethylaminoethyl)-1,2,3,4-tetrahydroquinoxalines (IVa, IVb, IVc, IVd).—A solution of 0.045 mole of the 2-(2-dialkylaminoethyl)-1,2,3,-4-tetrahydroquinoxaline and 0.1 mole of the isocyanate in 100 ml. of dry benzene was refluxed for two hours except in the case of IVc when the reaction mixture was merely heated to boiling. The solvent was removed by evaporation *in vacuo*, and the residue was triturated thoroughly with a mixture of benzene and 60–70° petroleum ether except with IVc. In this case the reaction mixture was cooled. The solid was filtered off and recrystallized from a benzene–petroleum ether (60–70°) mixture in the cases of IVa and IVb and from alcohol in the cases of IVc and IVd.

INDIANAPOLIS 6, INDIANA

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Restricted Rotation in Aryl Amines. XVI. 4-Substituted 1-Amino-2-methylnaphthalenes

BY ROGER ADAMS AND RAYMOND H. MATTSON[1]

RECEIVED APRIL 19, 1954

The optically active forms of N-benzenesulfonyl-N-carboxymethyl-1-amino-2-methylnaphthalene and its 4-chloro and 4-bromo derivatives have been synthesized. The relative racemization rates indicate that the halogen-substituted compounds are less stable than the unsubstituted, thus coinciding with the results found in analogous types of molecules. Nitration of N-benzenesulfonyl-1-amino-2-methylnaphthalene results in the formation of N-benzenesulfonyl-1-amino-2-methyl-4-nitronaphthalene.

In several previous papers, the relative rates of racemization of aromatic amines, in which restricted rotation between the nitrogen atom and the ring carbon is present, have been compared. The study of those compounds in which merely a single substituent in a fixed position has been modified has permitted speculation concerning the effect of size of the atom or group and/or of electronic changes upon stability of the molecule.[2] A sub-group in this

(1) An abstract of a thesis submitted by Raymond H. Mattson to the Graduate College of the University of Illinois, 1951, in partial fulfillment of the requirements for the Degree of Doctor of Philosophy; Eastman Kodak Company Fellow, 1947–1948; 1948–1949.

(2) (a) R. Adams and H. W. Stewart, THIS JOURNAL, **63**, 2859 (1941); (b) R. Adams and N. K. Sundholm, *ibid.*, **70**, 2667 (1948); (c) R. Adams and L. J. Dankert, *ibid.*, **62**, 2191 (1940); (d) R. Adams and A. A. Albert, *ibid.*, **64**, 1475 (1942); (e) R. Adams and J. R. Gordon, *ibid.*, **72**, 2454, 2458 (1950).