Quinazolines and 1,4-Benzodiazepines. XXIV.[1] Reaction of 1,4-Benzodiazepin-2-ones with Chloramine

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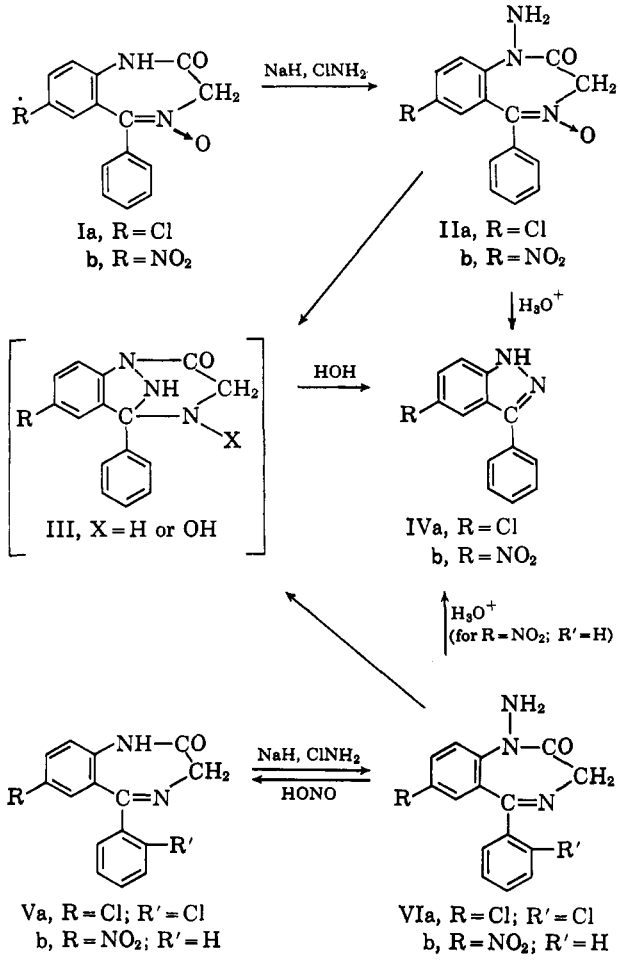
Our continued interest in the field of 1,4-benzodiazepines[1] led us to investigate the reaction of the lactams I and V with chloramine.

It has been reported in the literature[2,3] that pyridones and carbostyrils can be converted to their N-amino derivatives by treatment with chloramine in strongly alkaline aqueous solutions. However, this method appears to be of limited value, since the high pH values necessary to produce the amide anion accelerate the decomposition of chloramine.[4a]

SCHEME I



We have found that satisfactory yields of the 1-amino derivatives of type II and VI can be obtained by addition of an ethereal solution of chloramine to a solution of the sodium salt of the respective lactam in an inert solvent.[4b] By this method, it is also possible to transform acetanilide to the expected 1-acetyl-1-phenylhydrazine in 60–70% yield.

The reaction of compound Ia with chloramine gave a 60% yield of the 1-amino derivative IIa. Proof for the formation of a N–N bond was obtained by the hydrolysis of IIa to the known 5-chloro-3-phenylindazole IVa.[5] When the nitro derivative Ib was treated with chloramine, both the 1-amino compound IIb and the indazole IVb were isolated.[6] An intermediate represented by structure III could explain the facile hydrolysis of the primary reaction products II and VI to the indazoles IV during the work-up procedure.

The 1-amino diazepines VIa and VIb were obtained as indicated in Scheme I. Hydrolysis of VIb gave the indazole IVb which was found to be identical with an authentic specimen.[7]

Additional structure proof for compounds of type VI was obtained by deamination of VIa to Va with nitrous acid.[8] Furthermore, both benzylidene and monoacetyl derivatives of VIa were prepared.

The infrared spectra of compounds of types II and VI show a carbonyl absorption at 1700 cm.$^{-1}$, (starting materials at 1700 cm.$^{-1}$). The NH absorptions in compounds II and VI were at *ca.* 3340 (weak) and 3300 cm.$^{-1}$ (very weak) in contrast to the starting materials which showed a sharp band of medium intensity at 3400 cm.$^{-1}$.

Experimental

All melting points are corrected. The infrared spectra were determined in chloroform using a Beckman IR-9 spectrophotometer. Identity of compounds was proved by mixture melting point and comparison of infrared spectra.

Ethereal chloramine solutions were prepared according to published procedures.[9]

1-Acetyl-1-phenylhydrazine.—To a solution of 20 g. of acetanilide in 150 ml. of dimethylformamide was added 10.8 g. of a 50% suspension of sodium hydride in mineral oil. The solution was stirred and heated on a steam bath for 30 min. and cooled to 25°. After addition of 1500 ml. of 0.18 *N* solution of chloramine in ether the solution was left overnight. The solvents were removed *in vacuo* and the residue was dissolved in ethanol. On addition of petroleum ether (b.p. 30–60°), white needles formed which, after recrystallization from a mixture of ether and petroleum ether, had m.p. 123–125°, λ_{max}^{EtOH} 239 mμ (ε 5900),[10] ν_{CO} 1645 cm.$^{-1}$. The yield was 15 g. (67.5%).

1-Amino-7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide (IIa).—A solution of 4.6 g. (0.016 mole) of Ia[11] in 50 ml. of dimethylformamide was treated with 0.96 g. (0.02 mole) of a 50% suspension of sodium hydride in mineral oil and heated on a steam bath for 30 min. The mixture was allowed to cool to 25° before adding 125 ml. (0.017 mole) of a 0.14 *N* solution of chloramine in ether. The mixture was stirred for 16 hr. at room temperature and poured into ice–water. A solid was precipitated and collected on a filter. The ether layer was discarded. Recrystallization from a mixture of methylene chloride and benzene

(1) Paper XXIII: R. I. Fryer, G. A. Archer, B. Brust, W. Zally, and L. H. Sternbach, *J. Org. Chem.*, **30**, 1308 (1965).

(2) K. Hoegerle and H. Erlenmeyer, *Helv. Chim. Acta*, **39**, 1203 (1956).

(3) K. Hoegerle, *ibid.*, **41**, 539 (1958).

(4) (a) R. S. Drago, *J. Chem. Educ.*, **34**, 541 (1957); (b) The referee drew our attention to a paper by L. A. Carpino, *J. Org. Chem.*, **29**, 2820 (1964), which describes the preparation of a hydrazine-1,1-dicarboxylate using O-mesitoylhydroxylamine as aminating agent.

(5) K. Dziewonski and L. Sternbach, *Bull. intern. acad. polon.*, **A**, 333 (1935); *Chem. Abstr.*, **30**, 2972[4] (1936).

(6) In other cases, the presence of the corresponding indazoles in the mother liquors of products of type II and VI was shown by thin layer chromatography.

(7) W. Borsche and W. Scriba, *Ann.*, **540**, 96 (1939).

(8) This reaction has been observed on other N-amino heterocycles (see ref. 3) and is analogous to the deamination of 1,1-disubstituted hydrazines with nitrous acid: E. Fischer, *ibid.*, **199**, 314 (1879).

(9) W. Theilacker and E. Wegner, *Angew. Chem.*, **72**, 127 (1960).

(10) Reported values in the literature: m.p. 125°, W. F. Short, *J. Chem. Soc.*, **119**, 1446 (1921); λ_{max}^{EtOH} 238 mμ (ε 6000), N. I. Latosh and Z. V. Pushkareva, *Chem. Abstr.*, **55**, 8038*d* (1961).

(11) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

yielded 3.1 g. (64%) of IIa melting with decomposition at 225°, ν_{CO} 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{12}ClN_3O_2$: C, 59.71; H, 4.01; N, 13.93. Found: C, 59.93; H, 4.34; N, 13.65.

This compound (1 g.) was refluxed for 18 hr. in a mixture of equal volumes of methanol and concentrated hydrochloric acid to give 5-chloro-3-phenylindazole (IVa), which was identical with an authentic specimen.[5]

1-Amino-1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide (IIb).—To a solution of 9 g. (0.03 mole) of Ib[12] in 100 ml. of dimethylformamide was added 1.5 g. (0.031 mole) of a 50% suspension of sodium hydride in mineral oil. The solution was stirred for 30 min. at 25° after which time 365 ml. of a 0.11 *N* solution (0.04 mole) of chloramine in ether was added. After stirring the solution for 20 hr. at 25° it was poured into dilute sodium hydroxide and the ether layer was separated. The aqueous phase was extracted with methylene chloride. The organic layers were combined, washed free of alkali, and concentrated. The solid residue on recrystallization from benzene gave 1.9 g. (20%) of tan prisms melting at 200–203° dec., ν_{CO} 1700 cm.$^{-1}$ (IIb).

Anal. Calcd. for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 58.03; H, 4.00; N, 18.14.

Evaporation of the mother liquor of this product left a crystalline residue which, after recrystallization from benzene gave white prisms melting at 190–191°. The yield was 1.8 g. (25% of theory). This compound was identical with an authentic sample of 5-nitro-3-phenylindazole[7] (IVb).

1-Amino-7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one (VIa).—A solution of 25 g. (0.082 mole) of Va[13] in 250 ml. of tetrahydrofuran was treated with 5.0 g. (0.104 mole) of a 50% suspension of sodium hydride in mineral oil and heated on a steam bath for 15 min. The mixture was allowed to cool to 25° before adding 500 ml. of a 0.18 *N* solution (0.09 mole) of chloramine in ether. The mixture was then stirred for 16 hr. at room temperature.

The reaction mixture was poured into water and extracted with ether. The organic layers were washed with water, dried over sodium sulfate, and concentrated. The residue crystallized on addition of methanol to give white prisms which after recrystallization from methanol melted at 202–204°. The yield was 20.4 g. (78%), ν_{CO} 1690 cm.$^{-1}$ (VIa).

Anal. Calcd. for $C_{15}H_{11}Cl_2N_3O$: C, 56.27; H, 3.46; N, 13.12. Found: C, 55.94; H, 3.42; N, 13.07.

Addition of a molar amount of sodium nitrite in aqueous solution to an acetic acid solution of compound VIa gave a precipitate which, after recrystallization, was identified as Va.

Acetyl Derivative of VIa.—A solution of 5 g. of compound VIa in a mixture of 50 ml. of acetic anhydride and 50 ml. of pyridine was heated on a steam bath for 20 min. The solution was poured onto ice and the solid precipitate which formed was collected on a filter. Recrystallization from ether gave 3.7 g. (65%) of prisms melting at 221–223°.

Anal. Calcd. for $C_{17}H_{13}Cl_2N_3O_2$: C, 56.37; H, 3.62; N, 11.60. Found: C, 56.31; H, 3.81; N, 11.45.

Benzylidene Derivative of VIa.—A solution of 6 g. of compound VIa in 25 ml. of methanol, 25 ml. of pyridine and 10 ml. of benzaldehyde was heated under reflux for 18 hr. The reaction mixture was concentrated to a small volume, poured into water, and extracted with ether. The ether layer on concentration gave crystals which after recrystallization from ether yielded white prisms melting at 169–171°. The yield was 5.2 g. (68%).

Anal. Calcd. for $C_{22}H_{15}Cl_2N_3O$: C, 64.72; H, 3.70; N, 10.29. Found: C, 64.92; H, 4.00; N, 10.63.

1-Amino-1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one (VIb).—To a solution of 10 g. (0.036 mole) of Vb in 250 ml. of tetrahydrofuran was added 2.0 g. (0.042 mole) of a 50% suspension of sodium hydride in mineral oil. The mixture was stirred for 1 hr. at 25°, after which time 150 ml. of a 0.28 *N* solution (0.042 mole) of chloramine in ether was added. After stirring the solution for 19 hr. at 25° it was poured into ice-water. The ether layer was washed with 1 *N* aqueous sodium hydroxide and water and then it was dried with sodium sulfate. Evaporation of the ether gave a residue which crystallized on addition of ethanol.

Recrystallization from benzene gave 4.6 g. (44%) of yellow prisms melting at 155–157°, ν_{CO} 1700 cm.$^{-1}$ (VIb).

Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.80; H, 4.08; N, 18.91. Found: C, 60.53; H, 4.20; N, 19.00.

This compound (0.5 g.) was refluxed for 6 hr. in a mixture of methanol (10 ml.) and concentrated hydrochloric acid (10 ml.) to give 0.3 g. (74%) of 5-nitro-3-phenylindazole.[7]

Acknowledgment.—We are indebted to Dr. Al Steyermark and his staff for the microanalyses and Dr. V. Toome and Mr. S. Traiman for spectroscopic determinations.

(12) L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach, and N. Steiger, *J. Med. Chem.*, **6**, 261 (1963).

(13) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).

Quinazolines. I. The Structure of the Polychlorinated Products Obtained by the Phosphorus Pentachloride–Phosphorus Trichloride Chlorination of 2-Methyl-4-quinazolone and 2-Ethyl-4-quinazolone

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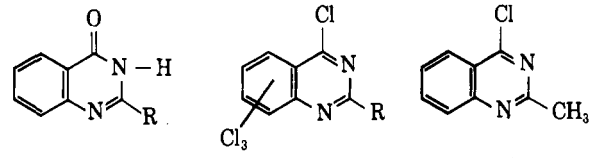
In 1890 Dehoff[2] reported that the chlorination of 2-methyl-4-quinazolone (I) with PCl_5–PCl_3 at 160° yielded a trichlorobenzo-2-methyl-4-chloroquinazoline (II) instead of the desired 2-methyl-4-chloroquinazoline (III). In 1909 Bogert and May[3] confirmed Dehoff's work and reported several unsuccessful attempts to obtain III by the chlorination of I under milder conditions.[4] Bogert and May also reported that a trichlorobenzo-2-ethyl-4-chloroquinazoline (V) is obtained by the chlorination of 2-ethyl-4-quinazolone (IV) with "a mixture of $POCl_3$–PCl_5."[5]



I, R = CH_3 II, R = CH_3 III

IV, R = C_2H_5 V, R = C_2H_5

To us it seemed quite improbable that an alkyl group in the 2-position of 4-quinazolone should have such a profound influence in activating the benzo ring toward nuclear chlorination. A more likely site for the introduction of the "extra" chlorines seemed to be the 2-alkyl substituents, and the n.m.r. spectra of the polychlorinated products clearly substantiate this contention.

(1) National Science Foundation Undergraduate Research Participant, 1963–1964.

(2) L. H. Dehoff, *J. prakt. Chem.*, [2] **42**, 354 (1890).

(3) M. T. Bogert and C. E. May, *J. Am. Chem. Soc.*, **31**, 507 (1909).

(4) H. C. Scarborough, B. C. Lawes, J. L. Minielli, and J. L. Compton [*J. Org. Chem.*, **27**, 957 (1962)] have accomplished the synthesis of III by the chlorination of I with $POCl_3$ in the presence of N,N-dimethylaniline.

(5) Some confusion exists concerning the actual composition of the chlorinating agent employed by Bogert and May. Although they claim to have followed Dehoff's procedure, their experimental procedure reports the use of $POCl_3$ in place of the PCl_3 employed by Dehoff. In our hands, the use of $POCl_3$–PCl_5 in place of PCl_3–PCl_5 in the chlorination of both I and IV led to extensive decomposition under conditions ranging from reflux temperature to 170° and no pure products could be isolated.