Metcalf Chemical Laboratories, Brown University

A Novel 7,6,5-Ring System: Triazolobenzoxazepinone

Clair G. Wood (I), Abel Geertsema (I), Linnea Freeburg (I), Edward J. Reardon (I),

Harold R. Jurgens (2) and Leallyn B. Clapp

A new ring system, a triazolobenzoxazepinone, has been synthesized in which the conformation of the 7-membered ring is rather rigidly imposed by the system. The conformation of the intermediates, nitro- and aminobenzoxazepinones, appear to be more sterically hindered than any precursors of the 7,6-ring system. The formation of the 7,6- and 7,6,5-ring systems and the preceding transition states must therefore be sterically accelerated through regulation of rotational conformation.

Negative groups at the 4-position on the aromatic ring I (Chart) were found essential in a previous study (3) for the anticipated ring closure of *N*-β-hydroxy derivatives of 2,6-dinitroanilines (II) by displacement of a nitro group to give substituted benzomorpholines (V). At the same time large groups, R and R', at the carbon α to the amino nitrogen in II (or an intermediate VI of the Jackson (4) type (5)) were found to be essential for the subsequent ring closure to V (6). These results suggest that the ring closure is only achieved by "steric acceleration through regulation of rotational conformation" (7) in the intermediate II, VI, or a transition state subsequent to II such as VII (closely related to the final product (V)). The large groups R and R' appear to force the wagging tail of the molecule out of the plane of the aromatic ring into favorable rotational conformations resembling the geometry of VII. Subsequent loss of the elements of nitrous acid from VII would lead to the final product (V). The experimental facts originally suggesting this sequence of events were that when R and R' were both H or one was C_2H_5 and the other H in II, no ring closure to benzomorpholines could be effected (3).

However, when Z is $-NO_2$ and Y is -COOH, $-COOCH_3$, -CN, or $-CONH_2$ (but not $-CF_3$ (3)) in I, a facile ring closure in the corresponding 2,4-dinitroanilines, II, occurs on the carboxylic acid function rather than displacement of the nitro group. A 7-membered ring, (III), a benzoxazepinone, is formed rather than a 6-membered benzomorpholine ring (V). The formation of the 7-membered ring (IIIa) is remarkable because it is formed in sodium methoxide solution (strong base) or in excess of 2-amino-2-methyl-1-propanol (weak base), reagents used in forming the benzomorpholines. The closure is the more remarkable because the ring IIIa opens readily in warm aqueous base and then closes in a new direction to displace a nitro group and form the 6-membered ring in Va.

Formation of the 7-membered ring in IIIa is a new example of the rather rare phenomena of steric hindrance accelerating a reaction (7, 8, 9). Here a sterically hindered starting compound II appears to favor formation of a still more hindered product, III.

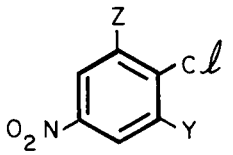
The nitro group in IIIa *ortho* to the amino function is reduced readily by ammonium sulfide solution to an amine IIIg and subsequently can be diazotized to a triazole ring, IVa. The 7-membered ring in this novel 7,6,5-triazolobenzoxazepinone ring system is easily opened in aqueous base and the potassium salt was isolated. The 7-membered ring snaps shut again to form IVa by back titration of the basic solution below *p*H 6.

Molecular models of compound IIIa suggests that the compound should not form easily if it were not, indeed, sterically accelerated by favorable conformational regulation in the transition state. When R and R' are both methyl the 7-membered ring is fairly rigid and the carbonyl group is crowded out of the plane of the conjugated system. In the laboratory, however, this crowding is not reflected in a shift of the carbonyl frequency in isolable compounds. The strong carbonyl band is exhibited at 1720 cm^{-1} in Ib, IIIa, and IVa and changes to a doublet at 1700 and 1715 cm^{-1} in both IIIf and IVf. The change from nitro to the amino group in the 9-position shifts the carbonyl frequency in both IIIg and IIIh to 1675 cm^{-1}.

In the previous work (3) the impossibility of isolating pure compounds of type II that could subsequently by cyclized to benzomorpholines was encountered. In the present benzoxazepinone series also most of the intermediates II could not be isolated because of contamination with III. However, one compound (IIf) was isolated in pure form and subsequently cyclized to IIIf in 95% yield. One borderline case in this respect appears to be IIe which was isolable in pure form but could not be cyclized to the corresponding IIIe under the same conditions where the closely related compound (IIIa) was formed in 50% yield from Id.

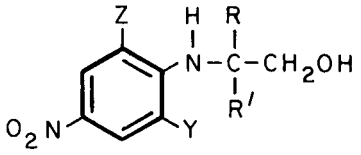
The triazole ring has been assigned an absorption peak at 1018 cm^{-1} in benzotriazole (10) which was in agreement with previous findings (3). In IVa, IVf, and the potassium salt derivative of IVa, peaks

were observed at 1012, 1002, and 1016 cm^{-1}, respectively. However, this absorption is not necessarily diagnostic for the triazole to the exclusion of other functions since absorptions of about the same medium intensity were observed in aminobenzoxazepinones IIIg at 1000 cm^{-1} and IIIh at 1005 cm^{-1}.



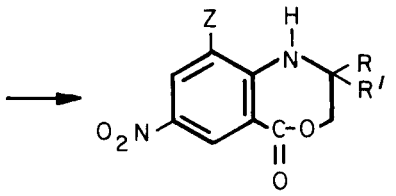
I

a. Y = COOH, Z = NO_2
b. Y = $COOCH_3$, Z = NO_2
c. Y = $CONH_2$, Z = NO_2
d. Y = CN, Z = NO_2



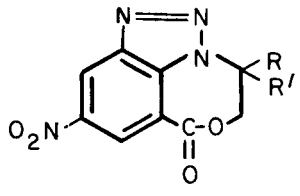
II

e. Y = CN, Z = NO_2, R = CH_3, R' = CH_2OH
f. Y = COOH, Z = NO_2, R = R' = H



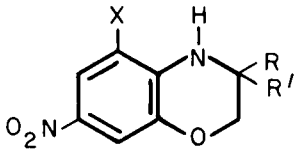
III

a. Z = NO_2, R = R' = CH_3
e. Z = NO_2, R = CH_3, R' = CH_2OH
f. Z = NO_2, R = R' = H
g. Z = NH_2, R = R' = CH_3
h. Z = NH_2, R = R' = H



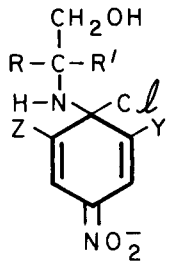
IV

a. R = R' = CH_3
f. R = R' = H

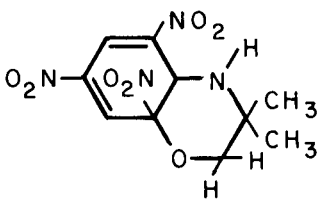


V

a. X = COOH, R = R' = CH_3



VI



VII

EXPERIMENTAL (11)

Derivatives of 3,5-dinitro-2-chlorobenzoic acid.

Nitration of 2-chlorobenzoic acid with potassium nitrate in concentrated sulfuric acid by the method of Ullmann (12) gave an 85% yield of 3,5-dinitro-2-chlorobenzoic acid (Ia), m.p. 196°. Ullmann reported a 94% yield, m.p. 198.5°.

Ib.

Methyl 2-chloro-3,5-dinitrobenzoate (13) m.p. 86.5°, was prepared in 72% yield from the corresponding acid chloride. The acid chloride, m.p. 62° (14), was prepared in 88% yield using phosphorus pentachloride (15). This two-step route to the ester used previously is not warranted since direct esterification of 2-chloro-3,5-dinitrobenzoic acid with a sulfuric acid catalyst gave a 96% yield of Ib. The devious routes to the chloro esters used by previous workers (16) seem to stem from a warning of Cohn (17) that the aromatic halogen was easily solvolyzed but this appears to be the case only in basic medium (18).

Ic.

The acid chloride was converted to 2-chloro-3,4-dinitrobenzamide (19), m.p. 180°, by refluxing with excess ammonium chloride in carbon tetrachloride in 58% yield. Using the conventional method of treating the acid chloride with aqueous ammonia gave as the main product, 3,5-dinitroanthranilic acid.

Id.

Dehydration of 2-chloro-3,5-dinitrobenzamide with thionyl chloride gave a 54% yield of 2-chloro-3,5-dinitrobenzonitrile (20), m.p. 139°, whereas phosphorus pentoxide or acetic anhydride gave lower yields.

2,4-Dinitro-6-cyano-(*N*-1,1-bis-hydroxymethylethyl)aniline (IIe) and 2-Methyl-2-hydroxymethyl-7,9-dinitro-1,2,3,5-tetrahydro-4,1-benzoxazepin-5-one (IIIe).

3,5-Dinitro-2-chlorobenzonitrile (2.57 g., 0.011 mole) was refluxed with 2.31 g. (0.022 mole) of 2-amino-2-methyl-1,3-propanediol in 50 ml. of anhydrous methanol for 30 minutes. Cooling followed by two recrystallizations from methanol gave 1.7 g. (55%) of 2,4-dinitro-6-cyano-(*N*-1,1-bis-hydroxymethylethyl)aniline, m.p. 163-165°. Prolonged refluxing of this compound with sodium methoxide in methanol did not effect a cyclization and only starting compound was recovered.

Anal. Calcd. for $C_{11}H_{12}N_4O_6$: C, 44.59; H, 4.08; N, 18.91. Found: C, 44.44; H, 4.30; N, 18.79.

By the procedure just described when the starting compound was 3,5-dinitro-2-chlorobenzamide, a 50% yield of the cyclic compound (IIIe), m.p. 187-188°, was obtained instead of the corresponding amide of type II. An analytical sample of the yellow compound was obtained by vacuum sublimation.

Anal. Calcd. for $C_{11}H_{11}N_3O_7$: C, 44.45; H, 3.73; N, 14.14. Found: C, 44.18; H, 3.55; N, 14.46.

N-(2-Hydroxyethyl)-3,5-dinitroanthranilic acid (IIf) and 7,9-Dinitro-1,2,3,5-tetrahydro-4,1-benzoxazepin-5-one (IIIf).

A solution of 3.0 g. (0.012 mole) of 2-chloro-3,5-dinitrobenzoic acid in 50 ml. of absolute methanol was refluxed with 1.5 g. (0.025 mole) of 2-aminoethanol for 45 minutes. Neutralization of the excess 2-aminoethanol with dilute hydrochloric acid precipitated 2.3 g. of IIf, m.p. 154-155.5°, 85%. An analytical sample of yellow crystals was obtained by simply drying the product in a vacuum desiccator.

Anal. Calcd. for $C_9H_9N_3O_7$: C, 39.86; H, 3.34; N, 15.50. Found: C, 39.86; H, 3.29; N, 15.71.

A different work-up procedure gave the cyclized product, IIIf, instead of the anthranilic acid. The methanol was removed and the residue was treated with excess concentrated hydrochloric acid. Heating on the steam bath for 0.5 hour gave IIIf in 95% yield. The analytical sample was obtained by recrystallization once from ethanol and once from ethyl acetate, m.p. 196.0-196.5°.

Anal. Calcd. for $C_9H_7N_3O_6$: C, 42.69; H, 2.79; N, 16.60. Found: C, 42.19; H, 2.58; N, 16.94.

2,2-Dimethyl-7,9-dinitro-1,2,3,5-tetrahydro-4,1-benzoxazepin-5-one (IIIa).

Twenty grams (0.08 mole) of 2-chloro-3,5-dinitrobenzoic acid and 30 g. (0.34 mole) of 2-amino-2-methyl-1-propanol were refluxed in 300 ml. of 1-butanol for 30 minutes. Cooling to -20° gave a yellow precipitate of the oxazepinone. Recrystallization from 900 ml. of ethyl acetate gave 15.1 g. (67%) of 2,2-dimethyl-7,9-dinitro-1,2,3,5-tetrahydro-4,1-benzoxazepin-5-one, m.p. 175-176° dec. A sublimed analytical sample had a m.p. 175.0-176.5° dec.

Anal. Calcd. for $C_{11}H_{11}N_3O_6$: C, 46.98; H, 3.94; N, 14.94. Found: C, 46.84; H, 3.85; N, 14.87.

2,2-Dimethyl-9-amino-7-nitro-1,2,3,5-tetrahydro-4,1-benzoxazepin-5-one (IIIg).

Twenty grams (0.07 mole) of IIIa was dissolved in 200 ml. of 95% ethanol at 50°. Ammonium sulfide (200 ml. of a 20% solution) was added in one portion and the mixture was kept at 45-50° for two hours while the mixture was stirred mechanically. Cooling and filtration gave 13.9 g. of brilliant orange crystals. Recrystallization from 1500 ml. of absolute methanol gave 12.7 g. (73%) of 2,2-dimethyl-9-amino-7-nitro-1,2,3,5-tetrahydro-4,1-benzoxazepin-5-one, m.p. 245-246° dec. The analytical sample was sublimed at 190°/1 mm.

Anal. Calcd. for $C_{11}H_{13}N_3O_4$: C, 52.58; H, 5.20; N, 16.72. Found: C, 52.68; H, 5.13; N, 16.30.

IIIh.

The homolog of IIIg, 9-amino-7-nitro-1,2,3,5-tetrahydro-4,1-benzoxazepin-5-one was obtained by a similar reduction of IIIf in 97% yield, m.p. 260° dec. The analytical sample was recrystallized from methanol and sublimed *in vacuo*.

Anal. Calcd. for $C_9H_9N_3O_4$: C, 48.43; H, 4.06; N, 18.83. Found: C, 48.53; H, 4.34; N, 18.64.

4,4-Dimethyl-9-nitro-3,4,5,7-tetrahydrotriazolo-[1,5,4-j,k]-4,1-benzoxazepin-7-one (IVa).

Five grams (0.02 mole) of IIIg was dissolved in 75 ml. of 20% sulfuric acid at 65° and then cooled to 0°. A cold solution of 1.5 g. (0.02 mole) of sodium nitrite in 30 ml. of water was added dropwise with stirring and the reaction mixture was kept at 0° for 2 hours. The mixture was poured into ice and the brown precipitate removed by filtration. Recrystallization from absolute ethanol and then benzene gave 2.1 g. (40%) of tan crystals. Vacuum sublimation gave an analytical sample of white crystals, m.p. 239-240°.

Anal. Calcd. for $C_{11}H_{10}N_4O_4$: C, 50.37; H, 3.84; N, 21.38. Found: C, 50.03; H, 3.84; N, 21.51.

IVf.

By the procedure described for the synthesis of IVa, 9-nitro-3,4,5,7-tetrahydrotriazolo-[1,5,4-j,k]-4,1-benzoxazepin-7-one, was prepared in 60% yield from IIIh. The sublimed analytical sample was light tan in color, m.p. 304° dec.

Anal. Calcd. for $C_9H_6N_4O_4$: C, 46.16; H, 2.58; N, 23.93. Found: C, 46.24; H, 2.98; N, 23.70.

One gram (0.004 mole) of IVa was dissolved in 50 ml. of 10% potassium hydroxide solution at 40°. The solution was warmed to 70° for 5 minutes and filtered. The *p*H was adjusted to 6.2 by addition of 20% hydrochloric acid. Two extractions with 75 ml. of 1-butanol gave one gram of tan residue. The residue was dissolved in 150 ml. of absolute ethanol and 0.73 g. (57%) of the potassium 5-nitro-1-(β-hydroxy-*t*-butyl)benzotriazole-7-carboxylate was precipitated by adding 500 ml. of benzene. The carbonyl absorption in the salt was at 1600 cm^{-1} in contrast to 1720 cm^{-1} in the benzoxazepinone, IVa.

Acidification of the original solution (below *p*H 6.2) gave 0.39 g. (39%) of IVa, accounting for 96% of starting material. The *p*H of 6.2 was critical in the isolation of potassium salt. The potassium salt crystallized with one molecule of water.

Anal. Calcd. for $C_{11}H_{13}N_4O_6K$: C, 39.27; H, 3.89; N, 16.65. Found: C, 39.00; H, 3.88; N, 16.26.

5-Carboxy-7-nitro-3,3-dimethylbenzomorpholine (Va).

A solution of one gram (3.6 mmole) of IIIa in 20 ml. of 10% potassium hydroxide and 60 ml. of methanol was refluxed for one hour. Cooling the red solution gave a dark orange precipitate which changed to yellow upon acidification with concentrated hydrochloric acid. The yellow product (0.43 g.) was collected and recrystallized from dilute methanol, m.p. 239-242°, 48%. An analytical sample was sublimed at 190°/1 mm., m.p. 243-245°, sinters 235°, carbonyl peak, 1675 cm^{-1}.

Anal. Calcd. for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.79; N, 11.11. Found: C, 52.40; H, 4.95; N, 11.18.

REFERENCES

(1) Taken in part from the MAT theses of C. G. Wood (1963), Abel Geertsema (1965), and the senior theses of Linnea Freeburg (1961) and Edward J. Reardon (1965). Supported in part by the National Science Foundation through its Academic Year Institute and Undergraduate Research Participation programs.

(2) Allied Chemical and Dye Fellow, 1957-1958.

(3) H. R. Jurgens, A. L. Burton, A. Eichenbaum, and L. B. Clapp, *J. Org. Chem.*, 25, 1710 (1960).

(4) C. L. Jackson and F. H. Gazzolo, *Am. Chem. J.*, 23, 376

(1900); C. L. Jackson and R. B. Earle, *ibid.*, 29, 89 (1903).
(5) Usually credited to J. Meisenheimer, *Ann.*, 323, 205 (1902).
(6) For nomenclature and numbering of ring systems, see R. G. Krupp and M. Kondas, *J. Chem. Educ.*, 35, 397 (1958). See also A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index", American Chemical Society, Washington, D. C., 1960, p. 234, No. 1819.
(7) Title of a paper on the Smiles rearrangement, J. F. Bunnett and T. Okamoto, *J. Am. Chem. Soc.*, 78, 5363 (1956).
(8) F. H. Westheimer and R. P. Metcalf, *ibid.*, 63, 1339 (1941).
(9) J. F. Bunnett and C. F. Hauser, *ibid.*, 87, 2214 (1965).
(10) L. W. Hartzel and F. R. Benson, *ibid.*, 76, 667 (1954).
(11) Melting points are uncorrected. Analyses were performed by S. M. Nagy, Microchem. Lab., MIT, Cambridge, Mass.
(12) F. Ullmann and G. Engi, *Ann.*, 366, 82 (1909).
(13) A. Purgotti and A. Contardi, *Gazz. Chim. Ital.*, 32, 1 526 (1902); *Chem. Zentr.*, 73, 2, 581 (1902).
(14) J. N. Ashley, W. H. Perkins, Jr., and R. Robinson, *J. Chem. Soc.*, 382 (1930).
(15) H. Lindemann and W. Wessel, *Ber.*, 58, 1221 (1925).
(16) A. B. Sen and R. C. Sharma, *J. Indian Chem. Soc.*, 33, 671 (1946); *ibid.*, 34, 877 (1957); F. Ullmann and S. M. Sane, *Ber.*, 44, 3730 (1911); B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, 1499 (1953).
(17) P. Cohn, *Monatsh. Chem.*, 22, 385 (1901).
(18) A. Purgotti and A. Contardi, *Gazz. Chim. Ital.*, 32, 1, 574 (1902); A. Purgotti and C. Lunini, *ibid.*, 32, 2, 324 (1903).
(19) E. B. Barnett, *Ber.*, 58, 1610 (1925).
(20) M. J. J. Blanksma, *Rec. Trav. Chim.*, [2], 20, 399 (1901).

Received October 1, 1965 Providence, Rhode Island 02912