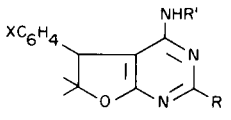
Synthesis of Substituted 2-Amino-3-Cyanodihydrofurans from Styrene Oxides and Malononitrile (1)

E. Campaigne, R. L. Ellis and Mary Bradford

The Chemistry Laboratories of Indiana University

The reaction of styrene oxides with the malononitrile anion leads to the formation of 2-amino-3-cyano-5-aryl-4,5-dihydrofurans (III), while a similar reaction with β,β-dimethylstyrene oxides leads to 2-amino-3-cyano-4-aryl-5,5-dimethyl-4,5-dihydrofurans (V). Therefore steric factors may play a significant role in the site of attack of the malononitrile anion on the oxide. Compounds of type V are more conveniently obtained from the cyanolactones (VI) by rearrangement and dehydration.

The cyclization of *o*-aminonitriles to form fused-ring pyrimidines has been a successful technique (2, *et seq.*). We have been exploring the synthesis of dihydrofuranopyrimidines of structure I, of possible interest as antimalarial agents, because of their structural relationship to



I

pyrimethamine and related antifols. A convenient synthesis of I could be devised from 2-amino-3-cyano-4-aryl-5,5-dimethyl-4,5-dihydrofuran (V) (see Scheme 1) as described previously (3). Some compounds of structure V may be prepared by cyclization of malononitriles having a tertiary γ-carbon (4), but overall yields from the starting ketone (e.g., isobutyrophenone) were low, and the method is limited to α-tertiary ketones and closely related types. Therefore it would be desirable to obtain these useful intermediates from other sources.

Since epoxides are known to open readily with nucleophilic reagents (5) and the reaction of unsymmetrical epoxides with cyanoacetic ester has been shown to produce cyanolactones (6), it seemed desirable to examine the reaction of malononitrile with epoxides (Scheme 1). Since Zuidema, *et al.*, (6) showed that the anion of cyanoacetic ester added exclusively at the primary carbon of styrene oxide, it was expected that malononitrile would give a similar result. However, the malononitrile anion is smaller than the cyanoacetic ester anion, and steric factors supply important controlling factors in this addition (7).

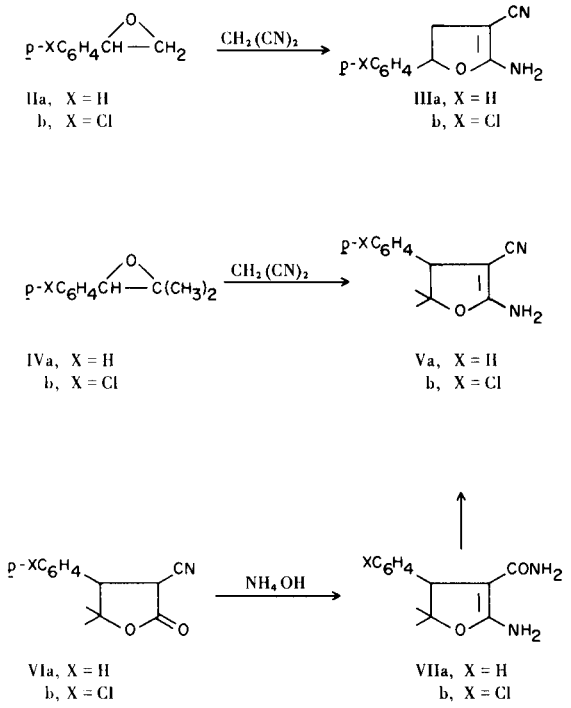
It was, therefore, necessary to examine the reactions of both styrene oxides and β,β-dimethylstyrene oxides, to determine the steric effects on this addition. In the latter case, the α-carbon would be less hindered and therefore more subject to attack by the anion. Substitution of an electron attracting group (e.g., chlorine) on the aromatic ring should enhance addition at the α-carbon, while electron-releasing groups (e.g., methyl) might slow the reaction, or even cause attack to occur at the more hindered β-carbon.

The results of our experiments are shown in Scheme 1. Reaction of the malononitrile anion with styrene oxide led to the isolation of 2-amino-3-cyano-5-phenyl-4,5-dihydrofuran (IIIa), the product of addition at the primary carbon. The structure of IIIa was confirmed by the presence of a proton quartet in the n.m.r. spectrum at 5.7 δ. This peak is characteristic of a benzylic proton adjacent to oxygen (8) and split by non-equivalent methylene protons, and is significantly different from the benzylic proton peak observed at 4.0-4.3 δ in 4-aryl-substituted 5,5-dimethyldihydrofurans (V). Similar results were obtained using *p*-chlorostyrene oxide.

A convenient synthesis of the desired tertiary epoxides IV, recently reported by Atkinson and Puttick (9), involved conversion of the ketone to the α-bromoketone, followed by a one-step borohydride reduction-cyclization to produce IV in yields averaging about 70%. An alternate synthesis based on epoxidation of the appropriate olefin was less satisfactory.

Conversion of IVa to Va was accomplished by treatment with the malononitirle anion, generated in dimethyl-

SCHEME I



sulfoxide with sodium hydride. The yield in this reaction was only 20%, but the isolated product was indeed Va, rather than the isomeric 5-phenyl-4,4-dimethyl derivative, as was shown by comparison to a sample of Va obtained from the cyanolactone VIa. Similarly, IVb was converted to Vb in 22% yield, and identity was again confirmed by comparison with a sample prepared from VIb *via* the amide VIIb.

The synthesis of compound V by the malononitrile synthesis involves five steps from the isobutyryl ketone (3) in overall yields of about 15-16%. The first four steps gave excellent yields, but the fifth step, dehydration of the amide to the nitrile, was poor (30-40%). The present sequence involves only three steps, but the overall yield was only 12-13%, indicating that the best sequence for synthesis of V involves the malononitrile synthesis of the cyanolactone, and a study of the dehydration of amides to nitriles could greatly improve this synthesis.

Steric effects have been shown to be important in the addition of malononitrile anion to styrene oxides. The anion attacks the least substituted carbon of the epoxide in each case, so that 5-aryldihydrofurans (III) are formed from simple styrene oxides, while 4-aryl-5,5-dialkyldihydrofurans (V) result from β,β-disubstituted styrene oxides.

EXPERIMENTAL

Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Indiana. Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord. The NMR spectra were recorded on a Varian Model A-60 spectrometer, using tetramethylsilane as an internal reference, in solvents specified, and are in agreement with structures assigned.

2-Amino-3-cyano-5-phenyl-4,5-dihydrofuran (IIIa).

Malononitrile (14.5 g., 0.22 mole) was dissolved in 125 ml. of DMSO and 5 g. of 58% sodium hydride was added over a period of 30 minutes during which time the temperature rose to 40°. The mixture was stirred for an additional 30 minutes, 12 g. (0.1 mole) of styrene oxide was added, the mixture was stirred at room temperature for 16 hours and heated at 60° for 3 hours. The cooled mixture was poured over ice, and the solid which formed was collected by filtration and taken up in chloroform. The solution was dried over anhydrous magnesium sulfate, filtered, decolorized with charcoal, and the chloroform was removed. The residue was recrystallized from benzene and hexane, to yield 10 g. (55%) of IIIa, m.p. 95-97°; λ max (potassium bromide) 2.90 (NH), 4.6 μ (CN); NMR (deuteriochloroform) δ 3.0 t (2H), 5.7 q (1H), 7.3 m (5H).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.94; H, 5.41; N, 15.04. Found: C, 70.94; H, 5.63; N, 15.05.

α-Bromo-*p*-chloroacetophenone.

p-Chloroacetophenone (100 g., 0.647 mole) was added to 475 ml. of glacial acetic acid in a 3-necked flask fitted with a stirrer, dropping funnel, and condenser, and 33.1 ml. (0.647 mole) bromine was added dropwise. The reaction mixture was poured into 1 l. of ice-water forming a thick, white suspension. The solid, white product was collected, taken up in chloroform, and the solution was washed with sodium bicarbonate until the aqueous layer was no longer acidic. The solution was dried over magnesium sulfate, filtered, and the solvent was evaporated to 1/3 its original volume. Upon cooling, 133 g. (88%) of white crystals formed, m.p. 95-97° as reported (10).

p-Chlorostyrene Oxide (IIb).

To 46.7 g. (0.2 mole) of α-bromo-*p*-chloroacetophenone in 200 ml. of tetrahydrofuran in a 3-necked flask fitted with a thermometer, dropping funnel, condenser, and stirrer, was added dropwise 11.4 g. (0.3 mole) of sodium borohydride in 100 ml. water and the mixture was then heated to a gentle reflux (65°) for 3 hours.

The flask was cooled, 10 g. (0.25 mole) of sodium hydroxide in 100 ml. water was added, and the mixture was again heated to reflux for 3 hours. The mixture was then cooled, the organic layer was separated, and the aqueous layer was extracted with ether. The organic layers were combined, dried over magnesium sulfate, filtered, and the solvents were evaporated. The liquid residue was vacuum distilled, yielding 27.8 g. (90%) of clear oil, collected from 107-115° (10.5 mm.) (11); I.R. (liquid film) no carbonyl band.

2-Amino-3-cyano-5-(*p*-chlorophenyl)-4,5-dihydrofuran (IIIb) (12).

Malononitrile (11.5 g., 0.175 mole) was added to 100 ml. of anhydrous DMSO in an ice-cooled 3-necked flask fitted with a thermometer, condenser, and stirrer, and 7.3 g. (0.175 mole) of sodium hydride (57.7% in mineral oil) was added over 45 minutes to maintain the temperature below 40°. *p*-Chlorostyrene oxide (11.2 g., 0.073 mole) was then added, and the mixture was

heated 3 hours at 65-75° with the internal temperature reaching 90° for about 0.5 hour. The mixture was cooled, poured into 1 l. ice-water forming a reddish solution with a tan precipitate, refrigerated 2 hours, and filtered. The solid product was washed well with water to remove the DMSO, then taken up in chloroform. The solution was washed with water, dried over magnesium sulfate, filtered, and the chloroform was evaporated completely. The resulting solid residue was dissolved in benzene, the solution was concentrated, and hexane was added to cause precipitation of 12.1 g. (75.3%) of a cream colored solid, m.p. 133-135°; I.R. λ max (potassium bromide) 2.9-3.1 μ, (-NH_2, 4.6 μ (-C≡N); NMR (pyridine-d_5): δ 7.31 s (4H), 5.58 q (1H), 4.97 s (1-2H), 3.05 m (2H).

Anal. Calcd. for $C_{11}H_9ClN_2O$: C, 59.87; H, 4.11; Cl, 16.07; N, 12.70. Found: C, 59.60; H, 4.43; Cl, 16.03; N, 12.51.

α-Bromoisobutyrophenone.

Isobutyrophenone (26 g., 0.17 mole) was placed in 125 ml. of glacial acetic acid and 27.2 g. of bromine was added dropwise. The mixture was stirred at room temperature for 5 hours, poured over ice, and the aqueous mixture was extracted with chloroform. The chloroform layers were combined and dried over anhydrous magnesium sulfate, filtered and the chloroform was removed, giving 35 g. (90%) of a lachrymatory oil, b.p. (2 mm.) 102-104° (13).

α-Bromo-*p*-chloroisobutyrophenone.

p-Chloroisobutyrophenone (125 g., 0.68 mole) was placed in 400 ml. of glacial acetic acid and 109 g. (38 ml.) of bromine was added dropwise. After the addition was completed, the mixture was stirred at room temperature for 4 hours, poured over ice, and extracted with chloroform. The organic layers were combined and dried over anhydrous magnesium sulfate, filtered, and the chloroform was removed. The residue was distilled, giving 142 g. (80%) of a lachrymatory oil, b.p. (0.5 mm.) 103-105°, which was used in the preparation of IVb without further purification.

2,2-Dimethyl-3-phenylethylene Oxide (IVa).

α-Bromoisobutyrophenone (30 g., 0.13 mole) was placed in 100 ml. of THF, and 6.08 g. (0.16 mole) of sodium borohydride in 50 ml. of water was added dropwise to the cooled THF solution. After the addition was complete, the mixture was stirred for 5 hours at room temperature and 5.5 g. of sodium hydroxide in 50 ml. of water was added dropwise. The mixture was stirred for 1 hour at 60°, cooled and extracted with ether. The ether layers were combined, dried over anhydrous magnesium sulfate, filtered, and the ether was removed. The residue was distilled, giving 13.5 g. (70%) of an oil, b.p. 91-93°; I.R. λ max (liquid film), 8.3, 11.1, 12.4 μ (C—O—C).

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.94; H, 8.14.

2,2-Dimethyl-3-(*p*-chlorophenyl)ethylene Oxide (IVb).

α-Bromo-*p*-chloroisobutyrophenone (28.9 g., 0.11 mole) was placed in 80 ml. of THF and 4.7 g. (0.12 mole) of sodium borohydride in 20 ml. of water was added dropwise. After the addition was completed, the mixture was stirred at 60° for 5 hours, then 5 g. (0.12 mole) of sodium hydroxide in 50 ml. of water was added, and the mixture was stirred an additional hour at 60°. The reaction mixture was cooled, the organic layer was separated, and the aqueous layer was extracted with ether. The organic layers were combined and dried over anhydrous magnesium sulfate, filtered, and the ether removed. The residue was distilled, giving 15 g. (75%) of an oil, b.p. (15 mm.) 123-127°; I.R. λ max (liquid film), 8.2, 11.1, 12.5 μ (C—O—C); NMR (deuteriochloroform) δ 0.95 s (3H), 1.35 s (3H), 3.73 s (1H), 7.19 s (4H).

Anal. Calcd. for $C_{10}H_{11}ClO$: C, 65.75; H, 6.07. Found: C, 65.51; H, 5.97.

2-Amino-3-carboxamido-4-phenyl-5,5-dimethyl-4,5-dihydrofuran (VIIa).

A heterogeneous mixture of 10.8 g. (0.05 mole) of α-cyano-β-phenyl-γ,γ-dimethylbutyrolactone (VIa) (3), and 50 ml. of concentrated ammonium hydroxide was stirred at room temperature for 45 minutes (solution occurred in about 10 minutes). The mixture was chilled in an ice bath for 15 minutes and the solid product was filtered, washed well with water and dried. The dry solid (dryness is most necessary since reversal of the rearranged product has been reported to occur in similar systems when treated with moist ethyl acetate) was recrystallized from ethyl acetate and cyclohexane to yield 10.3 g. (89%) of white crystals, m.p. 126-128°; I.R. λ max (potassium bromide), 2.88 (NH), 2.96 (NH), 3.10 (NH) and 6.04 μ ($CONH_2$); U.V. λ max (ethanol), 235 mμ (sh) (ε = 16,000) and 240 mμ (ε = 16,400); NMR (deuteriochloroform) δ 1.1 s (3H), 1.55 s (3H), 4.32 s (1H), 4.99 (broad), 7.3 m (5H).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.20; H, 6.94; N, 12.06. Found: C, 67.29; H, 7.00; N, 11.84

2-Amino-3-cyano-4-phenyl-5,5-dimethyl-4,5-dihydrofuran (Va).

From the Epoxide IVa.

A mixture of 6.2 g. of 58% sodium hydride (0.15 mole) and 8.6 g. of malononitrile (0.13 mole) in 100 ml. of DMSO was stirred for 2 hours, then 15 g. (0.1 mole) of IVa was added, and the solution was heated at 100° for 6 hours. After stirring overnight at room temperature the solution was poured over ice, some water was added, and the precipitate was collected and washed on the funnel with water. The crude sample melted at 130-133°. After recrystallization of the dried solid from benzene, 4.7 g. (20%) of white solid melting at 145-146.5° was obtained, which was identical with Va prepared from the amide VIIa.

From the Amino-amide VIIa.

To an oven-dried round bottom flask was added 35 ml. of anhydrous dimethylformamide. After warming to 50°, 2.32 g. (0.01 mole) of VIIa was added, followed by 1.43 g. (0.01 mole) of phosphorus pentoxide and 3.1 g. (0.03 mole) of triethylamine. The resulting mixture was warmed at 100° with stirring for 4 hours, cooled and poured over 120 ml. of iced water containing ca. 0.1 mole sodium carbonate. The pale yellow product was extracted with three 50 ml. portions of chloroform, washed with water and dried (potassium carbonate). Concentration at reduced pressure (sufficient to remove the triethylamine) afforded 2.8 g. of a yellow oil. The oil was chromatographed over 100 g. of silica gel and eluted with 1:1 chloroform-ether solvent. The first 400 ml. of eluate upon concentration at reduced pressure yielded the crude product which was recrystallized from ethyl acetate and hexane yielding 500 mg. of colorless crystals, m.p. 146-147°. Further elution afforded 500 mg. of starting material. Yield based on consumed starting material was 30%. I.R. λ max (potassium bromide), 2.90 (NH_2), 3.00 (NH_2), 4.56 (CN), 6.04 (1° NH_2) and 9.75 μ (COC); NMR (deuteriochloroform) δ 1.10 s (3H), 1.60 s (3H), 4.20 s (1H), 4.95 (broad), 7.31 m (5H).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.59; H, 7.11; N, 13.10.

2-Amino-3-carboxamido-4-(*p*-chlorophenyl)-5,5-dimethyl-4,5-dihydrofuran (VIIb).

A heterogeneous mixture of 38.0 g. (0.15 mole) of α-cyano-β-(*p*-chlorophenyl)-γ,γ-dimethylbutyrolactone (VIb) (3) and 150 ml. of concentrated ammonium hydroxide was stirred at room temperature for 3 hours, chilled in an ice-bath, filtered, washed well with water, air dried for 2 days and recrystallized from benzene yielding 36 g. (90%) of white crystals, m.p. 142-144°; I.R. λ max (potassium bromide), 2.85 (NH), 3.00 (NH), 3.20 (NH) and 6.05 μ ($CONH_2$); NMR (deuteriochloroform) δ 0.88 s (3H), 1.51 s (3H), 3.90 s (1H), 5.75 (broad) 7.35 d (4H).

Anal. Calcd. for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.67; H, 5.98; N, 10.40.

2-Amino-3-cyano-4-(*p*-chlorophenyl)-5,5-dimethyl-4,5-dihydrofuran (Vb).

From the Epoxide IVb.

To a cooled solution of 1.9 g. of sodium (0.08 mole) in 50 ml. of absolute ethanol was added dropwise, 5.3 g. (0.08 mole) of malononitrile in 30 ml. of absolute ethanol. After the addition was complete, 6.8 g. (0.037 mole) of IVb in 10 ml. of absolute ethanol was added dropwise. The mixture was heated to 60° for 3 hours, (white precipitate appeared after 10 minutes) and was stirred overnight at room temperature. The mixture was filtered, ethanol was removed from the filtrate, and the residue was taken up in ether and washed twice with water. The solid material collected from the reaction mixture by filtration was partially soluble in ether and partially soluble in water. The ether soluble material was combined with the ether soluble material from the filtrate and the solution was dried over anhydrous magnesium sulfate, filtered, and the ether was removed. The residue was recrystallized from benzene, yielding 2 g. (22%) of solid, m.p. 169-171°. This material was identical with that made by the dehydration of 2-amino-3-carboxamido-4-(*p*-chlorophenyl)-5,5-dimethyl-4,5-dihydrofuran, VIIb.

From the Amino-Amide VIIb.

To an oven-dried round bottom flask was added 3.5 g. (0.013 mole) of VIIb in 50 ml. of anhydrous dimethylformamide. This solution was warmed to 50° and 1.84 g. (0.013 mole) of phosphorus pentoxide and 4 g. (0.039 mole) of triethylamine were added. The reaction mixture was heated at 100° with stirring for 6 hours, then cooled and poured over a mixture of ice and sodium bicarbonate solution. The product was extracted with ether, washed with water and dried (magnesium sulfate). Concentration at reduced pressure yielded the crude product which, recrystallized from benzene, afforded 1.2 g. (37%) of colorless crystals, m.p. 170-171°. I.R. λ max (potassium bromide), 2.91 (NH_2), 3.00 (NH_2), 4.56 (CN), 6.05 (1° NH_2) and 9.80 μ (COC); NMR (deuteriochloroform): δ 0.85 s (3H), 1.52 s (3H), 4.00 s (1H), 4.90 m (2H), 7.17 m (4H).

Anal. Calcd. for $C_{13}H_{13}ClN_2O$: C, 62.78; H, 5.27; N, 11.26. Found: C, 62.72; H, 5.56; N, 11.00.

REFERENCES

(1) Contribution No. 1661 from the Chemical Laboratories of Indiana University. We gratefully acknowledge support of this investigation by the U. S. Army Medical Research and Development Command, Department of the Army, under Contract No. DA-49-193-MD-3004. This is Contribution No. 543 from the Army Research Program on Malaria.

(2) E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes and M. L. Hoefle, *J. Am. Chem. Soc.*, 81, 5711 (1960).

(3) E. Campaigne, R. L. Ellis, M. Bradford and J. Ho, *J. Med. Chem.*, 12, 000 (1969).

(4) E. Campaigne and R. L. Ellis, *J. Org. Chem.*, 32, 2372 (1967).

(5) S. Winstein and R. B. Henderson, "Heterocyclic Compounds", Vol. I, R. C. Elderfield, Ed., John Wiley, 1950. Chap. 1, p. 26.

(6) G. D. Zuidema, P. L. Cook and G. Van Zyl, *J. Am. Chem. Soc.*, 75, 294 (1953).

(7) E. E. Van Tamelen, G. Van Zyl and G. D. Zuidema, *ibid.*, 72, 488 (1950).

(8) L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy", MacMillan and Company, New York, 1959, p. 88.

(9) E. R. Atkinson and A. J. Puttick, *J. Med. Chem.*, 11, 1223 (1968).

(10) A. Collet, *Compt. Rend.*, 125, 718 (1897).

(11) S. L. Shapiro, H. Soloway and L. Freedman, *J. Am. Chem. Soc.*, 80, 6060 (1958).

(12) We are indebted to Mr. F. Gene DeBons, N. S. F. Undergraduate Research Participant, June-August, 1968, for the results of this experiment.

(13) K. V. Auwers and E. Lammerhirt, *Ber.*, 53, 428 (1920).

Received February 14, 1969 Bloomington, Indiana 47401