Studies on the Synthesis of Furan Compounds. XXX.[1] Syntheses and Steric Configurations of 3-(5-Nitro-2-furyl)-2-(5-bromo-2-furyl)acrylic Acid and Its Related Compounds[2]

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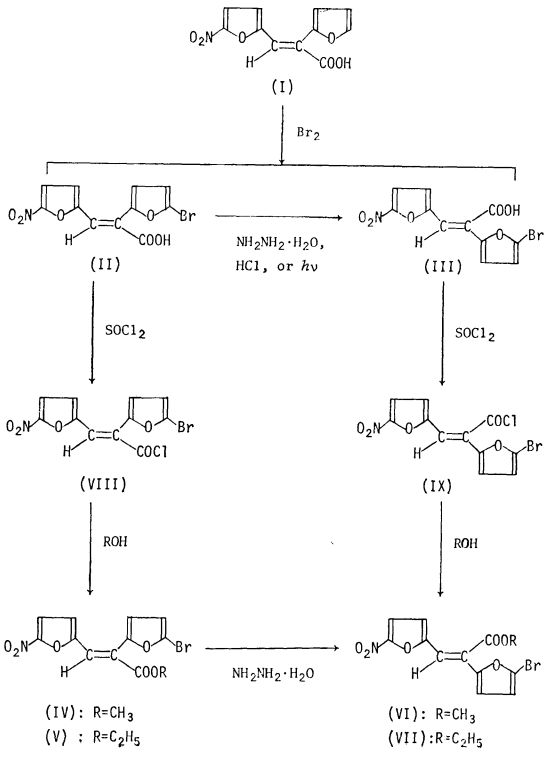
cis- and *trans*- 3-(5-Nitro-2-furyl)-2-(5-bromo-2-furyl)acrylic acids (II and III) and their functional derivatives have been synthesized in connection with the syntheses and steric configurations of 3-(5-nitro-2-furyl)-2-(5-bromo-2-furyl)acrylonitrile and its related compounds. The treatment of *cis*-3-(5-nitro-2-furyl)-2-(2-furyl)-acrylic acid (I) with bromine in refluxing carbon tetrachloride afforded a 1 : 1 mixture of II and III in quantitative yield. II and III afforded methyl (IV and VI) and ethyl (V and VII) esters, *via* each acid chloride (VIII or IX) by treatment with methanol and ethanol, respectively. Similarly, *cis*- and *trans*- 3-(5-nitro-2-furyl)-2-(5-bromo-2-furyl)acrylamides (X and XI) were obtained by treatment of VIII and IX with dry ammonia in benzene. Isomerization was observed in the conversion of X into *trans*-3-(5-nitro-2-furyl)-2-(5-bromo-2-furyl)-acrylonitrile (XII) upon treatment with phosphoryl chloride, while XI maintained its configuration under similar conditions to afford XII. On the other hand, *cis*-acid and esters (II, IV, and V) were converted into the corresponding *trans* isomers (III, VI, and VII) respectively, by treatment with hydrazine hydrate in refluxing methanol. II was confirmed to be isomerized to III by heating with hydrochloric acid or by irradiation with ultraviolet light (406 mμ). The structures and configurations of these compounds were discussed on the basis of their IR and NMR spectra.

cis-3-(5-Nitro-2-furyl)-2-(5-bromo-2-furyl)acrylonitrile has been prepared by bromination of both *cis*- and *trans*- 3-(5-nitro-2-furyl)-2-(2-furyl)acrylonitriles.[3] It could not be hydrolyzed to *cis*-3-(5-nitro-2-furyl)-2-(5-bromo-2-furyl)acrylic acid (II) by heating with 36% hydrochloric acid for 12 hr. Thus, bromination of 3-(5-nitro-2-furyl)-2-(2-furyl)acrylic acid has been carried out with the purpose of preparing II as a raw material in connection with the antibacterial properties of nitrofuran derivatives.[4-11] The present paper deals with the syntheses, steric configurations, and configurational interconversions of *cis*- and *trans*-3-(5-nitro-2-furyl)-2-(5-bromo-2-furyl)acrylic acids and their related compounds.

Results and Discussion

A mixture of *cis*- (II) and *trans*-3-(5-nitro-2-furyl)-2-(5-bromo-2-furyl)acrylic acid (III) was obtained quantitatively by treatment of *cis*-3-(5-nitro-2-furyl)-2-(2-furyl)acrylic acid (I) with an equimolar amount of bromine in refluxing carbon tetrachloride. It was confirmed to be a 1 : 1 mixture of II (48.9%) and III (51.1%) by NMR analysis, from which II and III were isolated in a 29.8% and a 33.1% yield, respectively, by fractional crystallization from aqueous methanol. In the IR spectra, a C=O stretching absorption appeared at 1690 cm^{-1} in II and at 1710 cm^{-1} in III. The NMR spectra of II and III revealed an olefinic proton signal at δ 7.39 and 6.88, respectively, indicating that the olefinic proton and COOH group are on one side of the ethylene double bond in the molecule of II. Methyl (IV and VI) and ethyl (V and VII) esters were obtained respectively by heating II and III with thionyl



Scheme 1.

1) Part XXIX of this series: I. Hirao, Y. Kato, Y. Fukano, and S. Yanai, This Bulletin, **46**, 1826 (1973).

2) Presented at the 27th Annual Meeting of the Chemical Society of Japan, Nagoya, October 13, 1972.

3) Y. Kato, T. Kuboyama, and I. Hirao, This Bulletin, **45**, 3165 (1972).

4) I. Hirao and Y. Kato, *Nippon Kagaku Zasshi*, **85**, 693 (1964); **86**, 633 (1965).

5) Y. Kato, Y. Hara, and I. Hirao, *ibid.*, **86**, 957 (1965).

6) Y. Kato and I. Hirao, *ibid.*, **87**, 1336 (1966).

7) I. Hirao, *ibid.*, **88**, 574 (1967); **89**, 713 (1968).

8) Y. Kato, H. Nakajima, and I. Hirao, *ibid.*, **89**, 955 (1968).

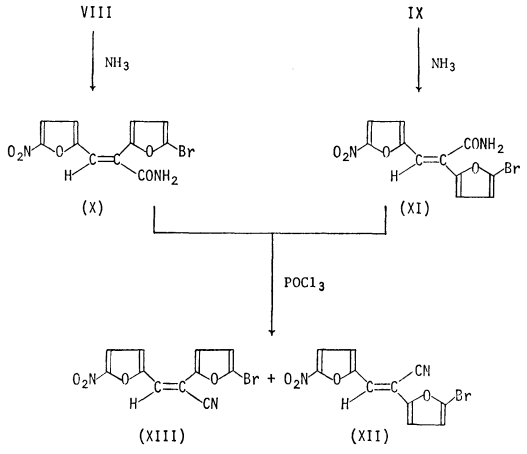
9) Y. Kato, This Bulletin, **44**, 489 (1971).

10) I. Hirao, Y. Kato, and T. Hirota, *ibid.*, **44**, 1923 (1971).

11) I. Hirao and Y. Kato, *ibid.*, **44**, 3136 (1971).

chloride in benzene and treating the resulting acid chlorides (VIII and IX) with methanol or ethanol. These esters were confirmed to retain the steric configuration of each mother acid by a comparison of the NMR spectra of IV and V with those of VI and VII. The olefinic proton signals in IV and V shifted to lower magnetic field than those in VI and VII; this suggests that IV and V are *cis*, and VI and VII are *trans*. In the IR spectra, *cis* esters also exhibited a C=O stretching absorption band at lower frequencies than the corresponding *trans* ester. In a comparison with the IR spectrum of IX, the *cis*-configuration of VIII was suggested by a shift to lower frequencies of the C=O stretching band to be similar to the relation observed between *cis* and *trans* forms of the acid and ester.

When VIII was treated with dry ammonia in benzene at room temperature, *cis*-3-(5-nitro-2-furyl)-2-(5-bromo-2-furyl)acryl amide (X) was obtained. Similarly, IX and ammonia produced *trans*-acrylamide (XI) in a good yield, indicating that the configurational interconversion did not take place in the reaction with ammonia under the conditions employed. Isomerization was observed in the dehydration reaction of X. On treatment with hot phosphoryl chloride, X afforded *trans*-3-(5-nitro-2-furyl)-2-(5-bromo-2-furyl)acrylonitrile (XII) as the main product, along with *cis*-acrylonitrile (XIII).[3] While XI maintained its *trans*-configuration giving rise to XII, a part of XI was changed the configuration to produce XIII. The structures of X and XI were supported by their IR and NMR spectra (see Experimental). The *trans*-configuration of XII is clearly shown by comparing its IR and NMR spectra with those of III and XIII.



Scheme 2.

When refluxed with 3/2 equimolar of hydrazine hydrate in methanol for 2 hr, 55% of II, 70% of IV, and 73% of V were respectively converted into III, VI, and VII. Similarly, 64% and 60% of II was isomerized to III on being heated with an equimolar amount of hydrochloric acid in methanol for 1.5 hr and by irradiation with UV light (406 mμ) for 25 hr. The conversion ratio was estimated on the basis of UV or NMR analysis.

Experimental

All the melting points are uncorrected. Elemental analyses were carried out with a Yanagimoto CHN Corder, MT-2 type. The IR spectra were taken on a JASCO IRA-2 grating infrared spectrophotometer by the KBr-disk method. The band positions are expressed in wave number, cm^{-1}. The UV spectra were performed on a Shimadzu photoelectric spectrophotometer, Model QV-50. UV-light irradiation and analyses were also carried out with the same apparatus. The NMR spectra were determined with a Japan Electron Optics Lab. JNM-C-60HL spectrometer. All the spectra were measured in DMSO-d_6 with a concentration of 2 mol% at 60 MHz, with HMDS as an internal reference; the chemical shifts are expressed in δ-values.

cis- *and* trans- *3-(5-Nitro-2-furyl)-2-(5-bromo-2-furyl)acrylic Acid (II and III).* A solution of bromine (50 g, 310 mmol) in carbon tetrachloride (100 ml) was slowly added to a stirred, warmed (70 °C) suspension of I (74.7 g, 300 mmol) in carbon tetrachloride (500 ml). The resulting mixture was then refluxed for 2 hr. After cooling, the precipitated product was filtered, washed with carbon tetrachloride (200 ml), and dried. Thus, 97.6 g (99.2%) of monobromo compound was obtained as brown-colored powder; mp 140—151 °C. The product was determined to be a mixture of II and III with the ratio of 48.9 : 51.1 by a comparison of NMR signal intensities. Fractional crystallization from methanol containing 20% of water afforded 29.3 g (29.8%) of II, 32.6 g (33.1%) of III, and 26.4 g of the recovered mixed-acid.

cis Acid (II); small orange needles, mp 187—189 °C. UV λ_{max}^{MeOH} mμ (ε): 227 (19400), 310 (11200), and 404 (11900). IR: 1690 (C=O). NMR (at 24 °C): 6.69 (d, 1H, J=3.8 Hz, bromofuran ring C_4–H), 6.83 (d, 1H, J=3.8 Hz, bromofuran ring C_3–H), 7.06 (d, 1H, J=4.1 Hz, nitrofuran ring C_3–H), 7.39 (s, 1H, olefinic proton), and 7.65 (d, 1H, J=4.1 Hz, nitrofuran ring C_4–H). Found: C, 40.60; H, 1.85; N, 4.26%. Calcd for $C_{11}H_6NO_6Br$: C, 40.24; H, 1.83; N, 4.27%.

trans Acid (III); brown granules; mp 175 °C. UV λ_{max}^{MeOH} mμ (ε): 305 (16400) and 406 (25100). IR: 1710 (C=O). NMR (at 24 °C): 6.69 (s, 2H, bromofuran ring C_3–H and C_4–H), 6.88 (s, 1H, olefinic proton), 6.96 (d, J=4.1 Hz, nitrofuran ring C_3–H), and 7.65 (d, 1H, J=4.1 Hz, nitrofuran ring C_4–H). Found: C, 40.16; H, 1.76; N, 4.11%. Calcd: the same value as II above.

cis- *and* trans- *3-(5-Nitro-2-furyl)-2-(5-bromo-2-furyl)acryloyl Chloride (VIII and IX).* A mixture of II or III (each 9.54 g, 30 mmol), thionyl chloride (3.6 g, 30 mmol), *N,N*-dimethylformamide (2 g) and dry benzene (300 ml) was stirred at 70 °C for 3 hr. The resulting solution was brought to dryness *in vacuo* and the residual acid chloride was washed with dry ether (50 ml). The crude chlorides were used in the subsequent experiments without further purification.

cis Acid chloride (VIII); brown powder, mp 137—139 °C. Yield: 9.8 g (97%). IR: 1740 (C=O).

trans Acid chloride (IX); brown powder, mp 97—100 °C. Yield: 9.6 g (95%). IR: 1790 (C=O).

Preparation of Esters (IV, V, VI and VII). VIII or or IX (each 3.4 g, 10 mmol) was dissolved in alcohol (10—20 ml) and the resulting solution was left standing at room temperature for a day. The precipitated product was filtered and recrystallized from alcohols to give pure esters.

cis Methyl ester (IV); brown plates (from methanol), mp 117—119 °C. Yield: 2.8 g (82%). IR: 1715 (C=O).

NMR (at 62 °C): 3.83 (s, 3H, O-CH_3), 6.72 (d, 1H, J=3.8 Hz, bromofuran ring C_4-H), 6.87 (d, 1H, J=3.8 Hz, bromofuran ring C_3-H), 7.09 (d, 1H, J=4.1 Hz, nitrofuran ring C_3-H), 7.44 (s, 1H, olefinic proton), and 7.64 (d, 1H, J=4.1 Hz, nitrofuran ring C_4-H). Found: C, 42.35; H, 2.68; N, 4.01%. Calcd for $C_{12}H_8NO_6Br$: C, 42.11; H, 2.38; N, 4.01%.

trans Methyl ester (V); ocherous needles (methanol), mp 106—107 °C. Yield: 2.5 g (73%). IR: 1720 (C=O). NMR (at 24 °C): 3.95 (s, 3H, O-CH_3), 6.73 (s, 2H, bromofuran ring C_3-H and C_4-H), 7.01 (s, 1H, olefinic proton), 7.03 (d, 1H, J=4.1 Hz, nitrofuran ring C_3-H), and 7.65 (d, 1H, J=4.1 Hz, nitrofuran ring C_4-H). Found: C, 42.02; H, 2.37; N, 4.02%. Calcd: the same value as IV above.

cis Ethyl ester (IV); ocherous needles (ethanol), mp 80—81 °C. Yield: 3.2 g (90%). IR: 1715 (C=O). NMR (at 62 °C): 1.31 (t, 3H, J=7.5 Hz, C-CH_3), 4.30 (q, 2H, J=7.5 Hz, O-CH_2-C), 6.73 (d, 1H, J=3.8 Hz, bromofuran ring C_4-H), 6.89 (d, 1H, J=3.8 Hz, bromofuran ring C_3-H), 7.09 (d, 1H, J=4.1 Hz, nitrofuran ring C_3-H), 7.43 (s, 1H, olefinic proton), and 7.64 (d, 1H, J=4.1 Hz, nitrofuran ring C_4-H). Found: C, 43.52; H, 2.51; N, 3.83%. Calcd for $C_{13}H_{11}NO_6Br$: C, 43.82; H, 2.81; N, 3.93%.

trans Ethyl ester (VII); brown cylinders (ethanol), mp 114—115 °C. Yield: 3 g (84.3%). IR: 1720 (C=O). NMR (at 75 °C): 1.31 (t, 3H, J=7.5 Hz, C-CH_3), 4.45 (q, 2H, J=7.5 Hz, O-CH_2-C), 6.73 (s, 2H, bromofuran ring C_3-H and C_4-H), 7.01 (s, 1H, olefinic proton), 7.03 (d, 1H, J=4.1 Hz, nitrofuran ring C_3-H), and 7.65 (d, 1H, J=4.1 Hz, nitrofuran ring C_4-H). Found C, 43.51; H, 2.84; N, 3.99%. Calcd: the same value as VI above.

cis- *and* trans- *3-(5-Nitro-2-furyl)-2-(5-bromo-2-furyl)acrylamide (X and XI).* To a stirred solution of VIII or IX (each 7 g, 20 mmol) in dry benzene (300 ml) was introduced dry ammonia. During the reaction, the temperature was kept below 30 °C. The resulting reaction mixture was filtered and the product was washed with water (200 ml) and then dried. Recrystallization from methanol afforded pure amides.

cis Amide (X); yellow needles, mp 181 °C. Yield: 6 g (81.5%). IR: 3350, 3160 (NH_2), and 1652 (C=O). NMR (at 24 °C): 6.73 (d, 1H, J=3.8 Hz, bromofuran ring C_4-H), 6.85 (d, 1H, J=3.8 Hz, bromofuran ring C_3-H), 6.95 (d, 1H, J=4.1 Hz, nitrofuran ring C_3-H), *ca.* 7.68 (broad s, 2H, NH_2), and 7.68 (d, 1H, J=4.1 Hz, nitrofuran ring C_4-H). Found: C, 40.65; H, 2.32; N, 8.22%. Calcd for $C_{11}H_7N_2O_5Br$: C, 40.37; H, 2.14; N, 8.56%.

trans Amide (XI): ocherous needles, mp 173—174 °C. Yield: 5.3 g (78%). IR: 3425—3040 (NH_2 and furan ring C-H) and 1661 (C=O). NMR (at 24 °C): 6.70 (d, 1H, J=3.8 Hz, bromofuran ring C_4-H), 6.72 (s, 1H, olefinic proton), 6.82 (d, 1H, J=3.8 Hz, bromofuran ring C_3-H), 6.93 (d, 1H, J=4.1 Hz, nitrofuran ring C_3-H), 7.72 (d, 1H, J=4.1 Hz, nitrofuran ring C_4-H), 7.83 (broad s, 1H, NH), and 8.20 (broad s, 1H, NH). Found: C, 40.20; H, 2.46; N, 8.35%. Calcd: the same value as X above.

cis- *and* trans- *3-(5-Nitro-2-furyl)-2-(5-bromo-2-furyl)acrylonitrile (XIII and XII).* A mixture of X or XI (each 3.3 g, 10 mmol), phosphoryl chloride (40—50 ml) and *N,N*-dimethylaniline (2 drops) was heated at 50—60 °C for 45 min. After cooling, the resulting mixture was poured into crushed ice with agitation. The solidified product was collected, washed with water, and dried. This was identified as a mixture of XII and XIII (63—65 : 37—35) by its NMR spectrum. Yield, 2.6—2.3 g (84—74%); mp 184—189 °C. The mixture was fractionally crystallized from methanol to afford 0.66 g (21.2%) of XII and 0.08 g (2.6%) of XIII.

trans Nitrile (XII); yellow powder, mp 164—166 °C. IR: 2230 (C≡N). NMR (at 97 °C): 6.77 (d, 2H, J= 3.8 Hz, bromofuran ring C_3-H and C_4-H), 7.23 (d, 1H, J= 4.1 Hz, nitrofuran ring C_3-H), 7.25 (s, 1H, olefinic proton), 7.64 (d, 1H, J=4.1 Hz, nitrofuran ring C_4-H). Found: C, 42.58; H, 1.61; N, 9.25%. Calcd for $C_{11}H_5N_2O_4Br$: C, 42.72; H, 1.62; N, 9.06%.

cis Nitrile (XIII); orange-red powder, mp 216 °C, undepressed on admixture with the authentic sample.[3] NMR (at 111 °C): 6.72 (d, 1H, J=3.8 Hz, bromfouran ring C_4-H), 6.90 (d, 1H, J=3.8 Hz, bromofuran ring C_3-H), 7.28 (d, 1H, J=4.1 Hz, nitrofuran ring C_3-H), 7.52 (s, 1H, olefinic proton), and 7.64 (d, 1H, J=4.1 Hz, nitrofuran ring C_4-H).

Conversion of II, IV, and V into III, VI, and VII. By Hydrazine Hydrate: A mixture of II, IV, or V (each 5 mmol), 80% hydrazine hydrate (0.47 g, 7.5 mmol), and methanol (100 ml) was stirred under reflux for 2 hr. The resulting solution was brought to dryness *in vacuo* and the residue was washed with water and then dried. A part of the residue was dissolved in DMSO-d_6 and the component ratio was determined by NMR. II was converted into III in 55% yield, IV into VI in 70%, and V into VII in 73%.

By Hydrochloric Acid: A mixture of II (1.64 g, 5 mmol), 36% hydrochloric acid (0.5 g), and methanol (100 ml) was refluxed for 1.5 hr. The resulting solution was brought to dryness *in vacuo*. Work-up as above afforded 64% of the conversion.

By UV-light Irradiation: A methanolic solution of II (10 μg/ml) was irradiated in a quartz cell with ultraviolet light (406 mμ) at room temperature for 25 hr. The conversion ratio was determined by the change of absorbance at 406 mμ. 60% of II was converted into III.