Studies on the Furan Series. Part VII. A Preparation of 2,3-Di(2-furyl and thienyl)furans

Seppo I. Pennanen

Department of Chemistry, Helsinki University of Technology, 02150, Otaniemi, Finland

Received January 31, 1977

Furoin reacts smoothly with dimethyl acetylenedicarboxylate *via* a Michael addition, which is followed by a dihydrofuran ring formation. After elimination of water the previously unknown 2,3-di(2-furyl)furan structure is produced. Thenoin gives a side reaction to yield a fumaric acid derivative in addition to the expected 2,3-di(2-thienyl)furan. A mechanism for the side reaction is suggested. The reactivities of the prepared new furan structures towards some oxidation, hydrogenation and electrophilic reagents were determined.

J. Heterocyclic Chem., 14, 745 (1977)

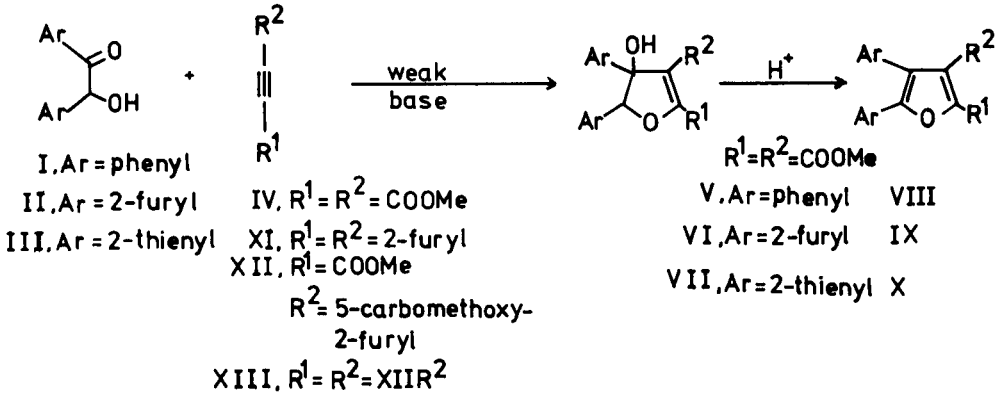
In the course of work (1) with furoin type acyloins it came to be of interest to study their reactions with acetylenic compounds. In literature (2), there is a short description of the reaction of benzoin with dimethyl acetylenedicarboxylate. Heteroaromatic acyloins (*e.g.* II and III) can be expected to react, like benzoin, with acetylenic triple bond *via* a Michael addition and cyclization to give a 4,5-dihydrofuran ring (*c.f.* V, Scheme 1). However, from the synthetic point of view the heteroaromatic rings should give more flexibility in subsequent transformations of the reaction products to other structures in contrast to the quite unreactive benzene rings of V or VIII.

The readily available acyloins furoin (II) and thenoin (III) were allowed to react with a number of acetylenic compounds (IV and XI-XIII). The only acetylenic compound reacting smoothly with II and III in the presence of a weak base was acetylenedicarboxylate (IV). The acetylenes XI-XIII were either unreactive or gave resinous material under the various conditions employed. Thus furoin II gave with IV predominantly the expected VI in 83% yield, and elimination of water occurred on treatment with acid to form the previously unknown 2,3-di(2-furyl)-furan structure IX in 89% yield. Thenoin (III) reacted with IV producing only 44% of VII due to a competing side reaction, which ruptured the bond between the thiophenic rings giving the compound XIV (*c.f.* Scheme 2) in 36% yield. The stability of XIV in refluxing toluenesulfonic acid/benzene indicated that XIV most probably exists in the (E)-configuration. An acid treatment of VII furnished smoothly X in 92% yield.

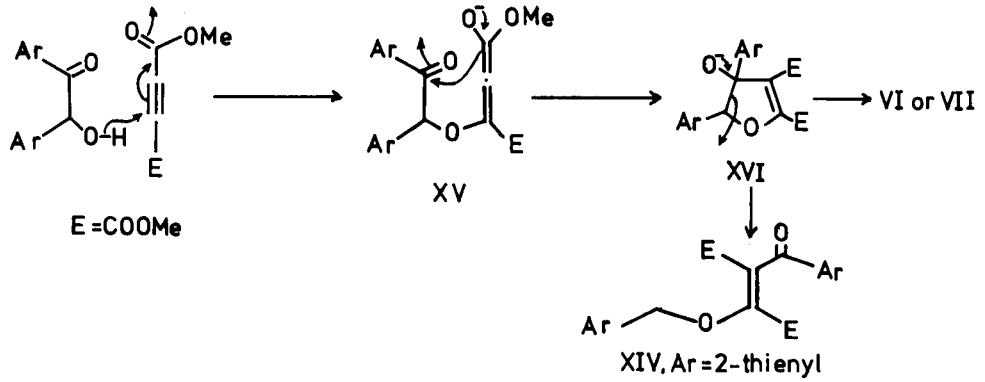
The explanation of the large difference in the reactivity of IV as compared to XI-XIII, presumably lies in the ability of an acetylenic compound to form an allenic intermediate XV (*c.f.* Scheme 2), in the first step of the Michael addition (2). Acetylenedicarboxylate IV (2) is known to give easily species such as XV, which facilitates the stabilization of the anion formed. In the compounds XI-XIII the allenic species will probably not be formed under the mild basic conditions used (strong bases react with II and III).

The mechanism for the formation of XIV can be rationalized as follows (*c.f.* Scheme 2). After cyclization, the species XVI can be protonated leading to VI or VII, but when Ar = 2-thienyl the rupture of the dihydrofuran ring can take place as well. The cleavage is presumably facilitated by the two adjacent thiophene rings, which pose a higher resonance energy than the furan rings of the species XVI (Ar = 2-furyl).

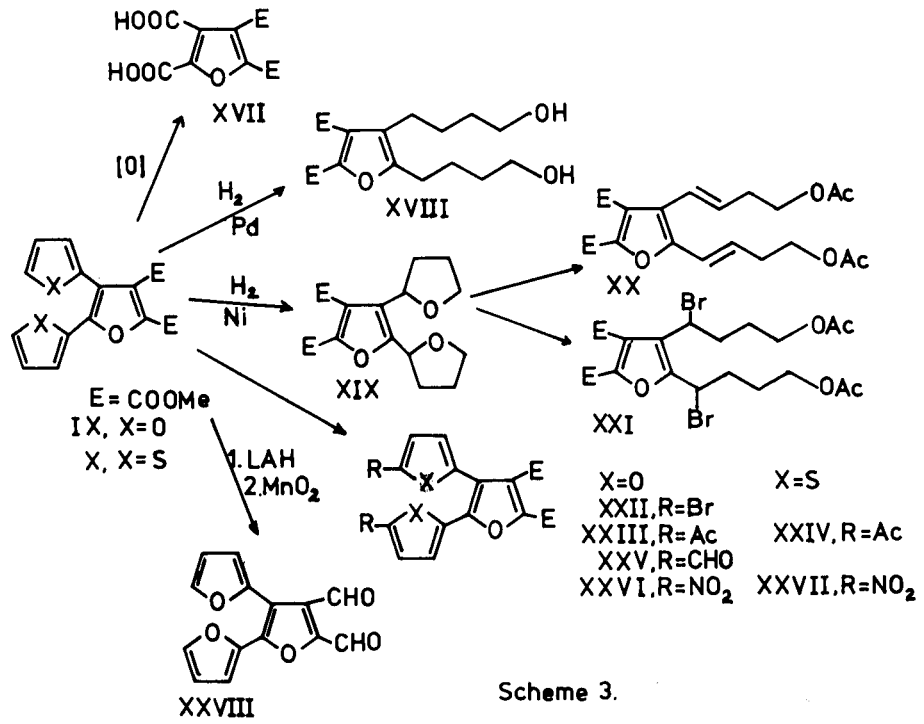
The compounds IX and X contain two electron with-



Scheme 1.



Scheme 2.



Scheme 3.

drawing ester groups, which stabilize the tetrasubstituted furan ring. This can be utilized in the transformation of the two other heterocyclic rings of IX to other systems. The stabilization is so effective that oxidation of IX with nitric acid gave XVII without any attack on the tetrasubstituted furan ring (*c.f.* Scheme 3). Furthermore hydrogenation took place cleanly in the monosubstituted rings giving XVIII or XIX in 98% and 97% yields, respectively, depending on the catalyst used. The tetrahydrofuran rings of XIX were readily opened to XX or XXI.

The monosubstituted heterocyclic rings of IX and X can be expected to be susceptible to an electrophilic attack because of their free 5-positions. The reactivity of IX and X towards some electrophilic reagents was tested. In every case disubstitution took place with orientations to the expected 5-positions only. Thus dibromination, diacetylation and diformylation of IX readily occurred in 87%, 67% and 46% yields, respectively. An interesting point is the facile formation of dinitro derivatives XXVI (68%) and XXVII (73%) on treatment with cupric nitrate/acetanhydride. Compound XXVI represents a new type of nitrofuran compound with a possible biological and medical interest.

A few attempts to modify the ester groups of IX to a more reactive form were made. The possibilities were greatly limited by the presence of the two monosubstituted sensitive furan rings. The best pathway found was a lithiumaluminiumhydride reduction followed by an active manganese dioxide oxidation to give XXVIII in 25% yield. Compound XXVIII contains the interesting, unsaturated 1,4-(Z)-dialdehyde structure, a precursor for many heterocycles. This otherwise quite labile moiety is so effectively stabilized by the close proximity of the heteroaromatic rings that XXVIII melts sharply at 105° without decomposition.

EXPERIMENTAL

Melting points are uncorrected. Spectral characteristics were recorded like reported in an earlier paper (1). Furoin and thenoin were prepared with methods published (1).

Di(2-furyl)acetylene (XI).

This compound was prepared from 1.00 g. of furoin *via* reduction (4) and semicarbazide/selenium dioxide treatment (6), yield 0.26 g. (31%), m.p. 21°; ir: 3130, 1490, 1455, 1205, 1145, 1005, 935, 880, 730 cm^{-1}; uv (ethanol) (ϵ): 250 (17500), 275 sh (22000), 282 (25000), 290 (26500) 297 sh (21500), 309 (17000) nm; nmr: δ 7.03 (2H, broad s), 6.20 (2H, broad s), 6.00 (2H, m); MS: m/e 158 (100%), 102 (62%), 76 (41%).

Anal. Calcd. for $C_{10}H_6O_2$: C, 75.95; H, 3.80. Found: C, 75.79; H, 3.61.

Dimethyl Acetylenedi(2-furyl-5-carboxylate) (XIII).

This compound was prepared from methyl 5-iodo-2-furoate (7) and methyl 5-acetyl-2-furoate (6,8,9); m.p. 187°; nmr: δ 7.15 (2H, d AB J 4.0 Hz), 6.75 (2H, d AB J 4.0 Hz), 3.83 (6H, s).

Anal. Calcd. for $C_{14}H_{10}O_6$: C, 45.41; H, 2.70. Found: C, 45.37; H, 2.65.

Dimethyl 4,5-Di(2-furyl)-4-hydroxy-(5*H*)dihydrofuran-2,3-dicarboxylate (VI).

Furoin (1.00 g., 5.2 mmoles) and 0.90 g. of acetylenedicarboxylate (IV, 6.30 mmoles) were refluxed with 0.70 g. of potassium carbonate in dry acetone for 12 hours. The base was filtered off and acetone was evaporated. Eluation with chloroform on preparative tlc plates gave 1.44 g. (83%) of a colourless, very viscous oil; ir: 3480, 1750-1630 cm^{-1}; nmr: δ 7.50-6.34 (6H, m), 5.77 (1H, s), 3.85 (3H, s), 3.66 (3H, s).

Anal. Calcd. for $C_{16}H_{14}O_8$: C, 57.49; H, 4.19. Found: C, 57.28; H, 4.08.

Dimethyl 4,5-Di(2-thienyl)-4-hydroxy-(5*H*)dihydrofuran-2,3-dicarboxylate (VII) and Dimethyl 2-Thenyloxy-2-thenoylfumarate (XIV).

Thenoin (III) (0.45 g.), 0.30 g. of IV and 0.20 g. of potassium carbonate were refluxed in dry acetone for 12 hours. After work-up and eluation on preparative tlc plates with chloroform two fractions (A and B) were obtained.

Fraction A.

This product (XIV) was obtained in 36% yield (250 mg.), m.p. 226° (from hexane/chloroform); ir: 1730, 1645, 730 cm^{-1}; nmr: δ 8.03 (2H, m), 7.70 (2H, m), 7.20 (2H, m), 5.33 (2H, s) 3.70 (3H, s), 3.57 (3H, s); uv (ethanol) (ϵ): 266 (20500), 292 (19500) nm; MS: m/e 366 (2%), 348 (3%), 303 (3%), 255 (4%), 238 (6%), 223 (2%), 111 (100%), 85 (8%), 83 (17%).

Anal. Calcd. for $C_{16}H_{14}O_6S_2$: C, 52.46; H, 3.83. Found: C, 52.41; H, 3.79.

Fraction B.

This product was obtained in 44% yield (320 mg.) of colourless, very viscous oil; ir: 3460, 1730, 1710 cm^{-1}; nmr: δ 7.30-6.80 (6H, m), 5.70 (1H, s), 3.83 (3H, s), 3.60 (3H, s), 3.50 (1H, broad s).

Anal. Calcd. for $C_{16}H_{14}O_6S_2$: C, 52.46; H, 3.83. Found: C, 52.22; H, 3.68.

Dimethyl 4,5-Di(2-furyl)furan-2,3-dicarboxylate (IX).

One drop of concentrated sulphuric acid was added to 500 mg. of VI in 10 ml. of methanol and the mixture was refluxed for 2 hours. After neutralization with aqueous sodium bicarbonate the product was isolated with preparative tlc giving 410 mg. (89%) of a pale yellow semisolid (IX), m.p. 69-70° (from ligroin/toluene); ir: 1730, 880, 870 cm^{-1}; uv (ethanol) (ϵ): 237 sh (13000), 245 (13300), 255 (13300), 274 (16500) 312 (13000), 328 (13800) nm; nmr: δ 2.42 (1H, d J 2.0 Hz), 2.51 (1H, d J 2.0 Hz), 3.07 (1H, d J 3.5 Hz), 3.22 (1H, d J 3.5 Hz), 3.50 (2H, m), 6.08 (6H, s); MS: m/e 316 (100%), 289 (46%), 287 (42%), 258 (27%), 229 (87%).

Anal. Calcd. for $C_{16}H_{12}O_7$: C, 60.76; H, 3.75. Found: C, 60.89; H, 3.75.

Dimethyl 4,5-Di(2-thienyl)furan-2,3-dicarboxylate (X).

After the treatment described above 230 mg. of VII gave 197 mg. (92%) of pale yellow solid, m.p. 85-86° (from hexane), ir: 1720 cm^{-1}; uv (ethanol) (ϵ): 231 (12000), 261 (11000), 323 (15000) nm; MS: m/e 348 (100%), 317 (19%), 290 (7%), 261 (14%), 203 (14%), 190 (12%), 111 (31%).

Anal. Calcd. for $C_{16}H_{12}O_5S_2$: C, 55.17; H, 3.45. Found: C, 54.91; H, 3.52.

Oxidation of IX.

Oxidation of 100 mg. of IX with nitric acid (10) and hydrolysis of the ester groups gave 65 mg. (83%) of the known furan-tetracarboxylic acid, m.p. 244-246°, lit. (11) m.p. 247°.

Hydrogenation of IX.

Two drops of concentrated sulphuric acid and 100 mg. of palladium(10%)/carbon catalyst were added to 500 mg. of IX in 100 ml. of methanol. The mixture was treated with hydrogen in a hydrogenation apparatus at room temperature for 15 hours. After removal of the catalyst, sulphuric acid and the solvent the residue was eluated on preparative tlc plates giving 510 mg. (98%) of dimethyl 4,5-di(4-butan-1-ol)-2,3-furandicarboxylate (XVIII) as a colourless, very viscous oil; ir: 3410, 2840, 1720 cm^{-1}; nmr: δ 3.80 (3H, s), 3.83 (3H, s), 3.56 (4H, broad t), 2.66 (2H, exchanged with deuterium oxide), 2.56 (4H, m).

Anal. Calcd. for $C_{16}H_{26}O_7$: C, 58.18; H, 7.88. Found: C, 57.69; H, 7.55.

Compound IX (500 mg.) was hydrogenated in neat methanol as above except that fresh Raney-nickel was used as a catalyst. Dimethyl 4,5-di(2-tetrahydrofuryl)-2,3-furandicarboxylate (XIX) was obtained (505 mg., 97%) as a colourless, very viscous liquid; ir: 1725 cm^{-1}; nmr: δ 4.97 (2H, m), 3.83 (6H, s), 3.80 (4H, m), 2.08 (8H, m).

Anal. Calcd. for $C_{16}H_{22}O_7$: C, 58.90; H, 6.75. Found: C, 58.71; H, 6.39.

Opening the Tetrahydrofuran Rings of XIX.

Compound XIX (150 mg.) and 300 mg. of tosyl acetate (4) were stirred at room temperature in dry acetonitrile for 24 hours. The solvent was evaporated and the residue eluated on preparative tlc plates to give 126 mg. (67%) of dimethyl 4,5-di[[4-[1-acetoxy-3-(E or Z)butenyl]]-2,3-furandicarboxylate (XX) as a very viscous oil; nmr: δ 6.50-5.70 (4H, m), 4.30-3.90 (4H, m), 3.90 (3H, s), 3.87 (3H, s), 2.70-2.20 (4H, m), 2.03 (6H, s).

Anal. Calcd. for $C_{20}H_{24}O_9$: C, 58.82; H, 5.88. Found: C, 58.39; H, 5.50.

Compound XIX (360 mg.) was treated under argon with magnesium bromide/acetic anhydride (12). Eluation on preparative tlc plates gave 280 mg. (43%) of very viscous dimethyl 4,5-di[4-(1-acetoxy-4-bromobutyl)]-2,3-furandicarboxylate (XXI); nmr: δ 5.15 (2H, m), 4.08 (4H, t J 7.0 Hz), 3.83 (6H, s), 2.00 (6H, s), 2.30 (4H, broad t J 7.0 Hz), 2.10-1.50 (4H, m); MS: m/e 491 (10%), 489 (11%), 409 (100%), 377 (96%), 349 (56%), 335 (69%), 317 (66%), 275 (96%), 258 (40%), 257 (99%), 243 (41%), 217 (39%), 203 (44%).

Anal. Calcd. for $C_{20}H_{26}Br_2O_9$: C, 42.11; H, 4.56. Found: C, 41.79; H, 4.21.

Dimethyl 4,5-Di(5-bromo-2-furyl)-2,3-furandicarboxylate (XXII).

Compound IX (500 mg.) was dissolved in 40 ml. of dry methylene chloride. At 0° and in the dark, 0.20 ml. (equivalent) of bromine in 5 ml. of methylene chloride was added dropwise. After removal of solvent and eluation on preparative tlc plates, a pale yellow solid was obtained, yield, 640 mg. (87%), m.p. 93-94° (from hexane); nmr: δ 6.86 (1H, q AB J 3.5 Hz), 6.69 (1H, q AB J 3.5 Hz) 6.43 (1H, q AB J 3.5 Hz), 6.35 (1H, q AB J 3.5 Hz), 3.92 (3H, s), 3.88 (3H, s); uv (ethanol) (ε): 284 (18,000), 339 (15,500) nm; MS: m/e 476 (47%), 474 (90%), 472 (47%), 396 (94%), 394 (100%), 367 (93%), 365 (91%), 286 (16%), 258 (21%).

Anal. Calcd. for $C_{16}H_{10}Br_2O_7$: C, 40.54; H, 2.13. Found: C, 40.28; H, 2.08.

Dimethyl 4,5-Di(5-acetyl-2-furyl)-2,3-furandicarboxylate (XXIII).

Compound IX (200 mg.) was refluxed with excess of tosyl acetate in dry acetonitrile for 24 hours (8). Preparative tlc treatment gave a pale yellow solid (XXIII), yield, 172 mg. (67%), m.p. 153° (from ligroin/chloroform); ir: 1730, 1715, 1670, 1655 cm^{-1}; nmr: δ 7.23 (4H, s), 4.00 (3H, s), 3.93 (3H, s), 2.47 (3H, s), 2.44 (3H, s); uv (ethanol) (ε): 280 sh (22,500), 290 (28,000), 350 sh (19,000), 360 (19,500), 380 sh (13,000) nm; MS: m/e 400 (100%), 329 (30%), 285 (29%).

Anal. Calcd. for $C_{20}H_{16}O_9$: C, 60.00; H, 4.00. Found: C, 59.92; H, 3.91.

Dimethyl 4,5-Di(5-formyl-2-furyl)-2,3-furandicarboxylate (XXV).

The Vilsmeyer-reagent was prepared (13) using dry DMF as the solvent. Compound IX (100 mg.) was heated in the reagent under argon at 80-90° for 2 hours. The reported work-up procedure (13) was followed. The purification of XXV was performed by preparative tlc, yield, 53 mg. (46%) of pale yellow solid, m.p. 181° (from ligroin/chloroform); ir: 1720, 1700, 1640 cm^{-1}; uv (ethanol) (ε): 289 sh (28,500), 297 (30,500), 355 sh (20,500), 370 (22,500), 390 sh (14,500) nm; nmr: δ 9.50 (1H, s), 9.43 (1H, s), 7.30 (4H, s), 4.02 (3H, s), 3.95 (3H, s); MS: m/e 372 (100%), 344 (76%), 315 (23%), 299 (10%), 282 (25%), 280 (23%), 249 (27%), 213 (23%).

Anal. Calcd. for $C_{18}H_{12}O_9$: C, 58.06; H, 3.23. Found: C, 57.97; H, 3.14.

Dimethyl 4,5-Di(5-acetyl-2-thienyl)-2,3-furandicarboxylate (XXIV).

Compound X (130 mg.) was treated with tosyl acetate as described above; yield 60 mg. (38%) of pale yellow solid, m.p. 178° (from ligroin/chloroform); ir: 1735, 1705, 1650 cm^{-1}; uv (ethanol) (ε): 259 (11,000), 292 (14,500), 343 (15,800) nm; nmr: δ 7.83 (1H, d J 3.0 Hz), 7.75 (1H, d J 3.0 Hz), 7.40 (1H, d J 3.0 Hz), 7.30 (1H, d J 3.0 Hz), 3.90 (3H, s), 3.73 (3H, s), 2.57 (3H, s), 2.50 (3H, s); MS: m/e 432 (62%), 417 (57%), 155 (24%), 153 (81%), 111 (100%).

Anal. Calcd. for $C_{20}H_{16}O_7S_2$: C, 55.56; H, 3.70. Found: C, 55.50; H, 3.61.

Dimethyl 4,5-Di(5-nitro-2-furyl)-2,3-furandicarboxylate (XXVI).

Compound IX (500 mg.) was treated with cuprous nitrite/acetic anhydride reagent (14) at room temperature. After work-up and eluation on preparative tlc plates, a greenish yellow solid (XXVI) was obtained, yield 440 mg. (68%), m.p. 177° (from ethyl acetate); ir: 1755, 1725, 1520, 1500, 830 cm^{-1}; uv (ethanol) (ε): 234 (16,500), 249 (15,000), 318 (15,500), 380 (18,000) nm; nmr: δ 7.43 (1H, d), 7.40 (2H, s), 7.27 (1H, d), 4.03 (3H, s), 3.93 (3H, s); MS: m/e 406 (100%), 373 (16%), 333 (13%), 332 (74%), 328 (13%), 243 (19%).

Anal. Calcd. for $C_{16}H_{10}N_2O_{11}$: C, 47.29; H, 2.46; N, 6.70. Found: C, 47.11; H, 2.30; N, 6.59.

Dimethyl 4,5-Di(5-nitro-2-thienyl)-2,3-furandicarboxylate (XXVII).

Compound X (100 mg.) was treated with cuprous nitrite/acetic anhydride reagent as described above, yield, 90 mg. (73%) of yellow solid, m.p. 168° (from chloroform); ir: 1740, 1720, 1520, 1500, 810 cm^{-1}; uv (ethanol) (ε): 263 (15,000), 300 (16,000), 369 (18,500) nm; nmr: δ 7.90 (2H, m), 7.40 (2H, m), 3.90 (6H, broad s); MS: m/e 438 (51%), 360 (14%), 281 (17%), 156 (10%), 147 (11%), 100 (30%), 98 (33%), 86 (46%), 85 (70%), 83 (100%).

Anal. Calcd. for $C_{16}H_{10}N_2O_9S_2$: C, 43.84; H, 2.28; N, 6.40. Found: C, 43.69; H, 2.08; N, 6.25.

4,5-Di(2-furyl)-2,3-furandialdehyde (XXVIII).

Compound IX (500 mg.) was reduced with LAH in dry ether. The reaction product was not purified, but the crude diol was oxidized with an excess of active manganese dioxide (15) in 50 ml. of dry refluxing benzene. After 24 hours manganese dioxide was filtered off and the residue was concentrated and eluated on preparative tlc plates, yield, 102 mg. (25%) of XXVIII, a pale yellow solid, m.p. 105° (from hexane/chloroform); ir: 1680, 1665 cm^{-1}; uv (ethanol) (ε): 249 (12,500), 283 (12,000), 339 sh (5,900), 345 (6,100) nm; nmr: δ 10.30 (1H, s), 10.00 (1H, s) 7.50 (2H, broad s), 6.80 (2H, m), 6.50 (2H, m); MS: m/e 256 (100%), 228 (55%), 200 (10%), 199 (28%), 171 (54%), 149 (18%).

Anal. Calcd. for $C_{14}H_8O_5$: C, 65.63; H, 3.13. Found: C, 65.48; H, 2.97.

Acknowledgement.

The author is greatly indebted to Professor J. Gripenberg and Associate Professor T. Hase for their helpful comments and suggestions.

REFERENCES AND NOTES

(1) S. I. Pennanen, *Acta Chem. Scand.*, 27, 3133 (1973).

(2) J. B. Hendrickson, R. Rees, and J. F. Templeton, *J. Am. Chem. Soc.*, 86, 107 (1964).

(3) G. Märkl, *Chem. Ber.*, 3005 (1961).

(4) M. H. Karger and Y. Mazur, *J. Am. Chem. Soc.*, 90, 3878 (1968).

(5) T. L. Ho and C. M. Wong, *Synthesis*, 161 (1975).

(6) I. Lalezari and A. Shafiee, *Tetrahedron Letters*, 5105 (1969).

(7) N. K. Kochetkov and E. E. Nafant'ev, *Vestnik. Mosk. Univ. Ser. Mat., Mekh., Astron., Fiz., Khim.*, 13, 119 (1958); *Chem. Abstr.*, 53, 12267i (1959).

(8) S. I. Pennanen, *Heterocycles*, 4, 1021 (1976).

(9) R. D. Stephens and C. C. Castro, *J. Org. Chem.*, 28, 3313 (1963).

(10) D. M. Carbateas and G. L. Williams, *J. Heterocyclic Chem.*, 11, 819 (1974).

(11) T Reichstein, A. Grüssner, K. Schindler and E. Hardmeier, *Helv. Chim. Acta*, 16, 280 (1933).

(12) D. J. Goldsmith, E. Kennedy and R. G. Campbell, *J. Org. Chem.*, 40, 3571 (1975).

(13) H. W. Moore and H. R. Snyder, *J. Org. Chem.*, 29, 97 (1964).

(14) A. G. Anderson, J. A. Nelson and J. J. Tozuma, *J. Am. Chem. Soc.*, 75, 4980 (1953).

(15) I. M. Goldman, *J. Org. Chem.*, 34, 1979 (1969).