Studies on Heteroaromaticity. LII.[1] Syntheses and Reactions of α-Acetylenic Ketones Containing Nitrofuran Ring

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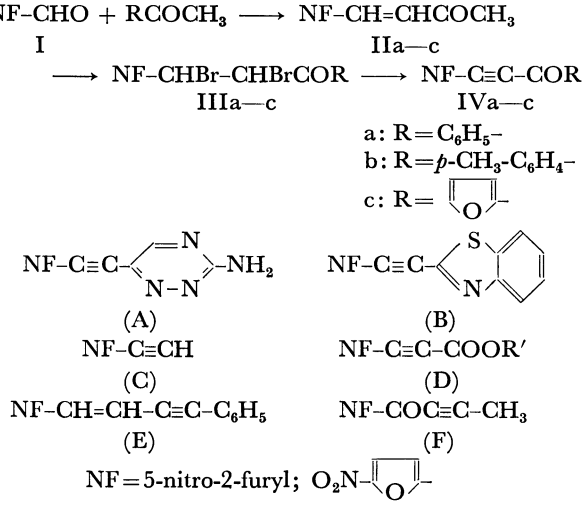
2-(5-Nitro-2-furyl)-1-phenyl- (IVa), -*p*-methylphenyl- (IVb) and -(2-furyl)-acetylene (IVc) were prepared by condensation of nitrofurfural with the corresponding aryl methyl ketones, followed by bromination and dehydrobromination. Addition of aniline and cyclohexylamine to IVa afforded simple adducts Va and VIa respectively. Treatment of IVa,b with hydroxylamine, hydrazine hydrate, semicarbazide and benzamidine gave isoxazoles (VIIIa,b), pyrazoles (VIIIa,b), 1-carbamidopyrazoles (IXa,b) and pyrimidines (Xa,b) respectively. When treated with benzonitrile oxide at room temperature, IVa afforded isoxazole XIa together with furoxan, but the thermal 1,3-dipolar reactions of IVa,b with 5-nitro-2-furocarbonitrile oxide afforded exclusively isoxazoles XIIa,b. For comparison, 5-nitro-2-furfurylidenebenzophenone (IIa) was treated with benzonitrile oxide at room temperature to afford an isomeric mixture of the isoxazolines XIIIa and XIVa together with furoxan. Similar treatment of 5-nitro-2-furfurylideneacetone afforded similar results affording a mixture of XV and XVI together with furoxan. When treated with phenacylpyridinium ylide, IVa,b afforded pyrrocolines XVIIa,b. The structural elucidation of the products was carried out on the basis of the spectral data.

Saikawa *et al.*,[2] Yoshina *et al.*[3] and Sasaki and Shoji[4] reported independently on the preparation of 3-amino-6-[2-(5-nitro-2-furyl)ethynyl]-1,2,4-triazines (A), 2-(5-nitro-2-furyl)ethynylbenzothiazole (B) and 5-nitro-2-furylacetylene (C) and -propiolate (D). Saikachi and Sugimoto presented the synthesis of 3-(5-nitro-2-furoyl)prop-2-yne (E)[5] and Saikachi *et al.* that of 1-phenyl-4-(5-nitro-2-furyl)but-3-ene-1-yne (F),[6] but detailed experimental data have not been published yet. This paper deals with the syntheses of 2-(5-nitro-2-furyl)-1-aroylacetylenes (IV), another type of α-acetylenic nitrofuran, from 5-nitro-2-furfural (I) according to a sequence of the following reactions:

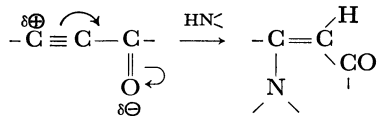


Since these α-acetylenic ketones belong to activated acetylenes,[7] several nucleophilic additions involving the 1,3-dipolar cycloaddition to amines were carried out.

Results and Discussion

Preparation of α-Acetylenic Ketones (IVa—c). In a previous paper,[8] we reported the synthesis and some reactions of the dibromide IIIa, in which we postulated the intermediacy of 2-(5-nitro-2-furyl)-1-benzoylacetylene (IVa) in the preparation of 3-(5-nitro-2-furyl)-5-phenyl-1*H*,2-pyrazole from IIIa and hydrazine hydrate. To verify this assumption, IIIa was treated in benzene with triethylamine at room temperature to afford IVa as expected. Similar treatments were applied to other dibromides IIIb,c and all afforded the corresponding acetylenic ketones IVb,c in good yields. The yields, spectral data and analyses are summarized in Table 1. The presence of a triple bond in IV is demonstrated by the appearance of $\nu_{C\equiv O}$ at 2260—2280 cm^{-1} in the IR spectra and by the hypsochromic shifts of the UV spectra from the corresponding double bonded compounds as observed by a comparison of IVb with IIb (see Experimental). Another IR spectral feature is observed in comparison of $\nu_{C=O}$; $\nu_{C=O}$ in IVb at 1620 cm^{-1} is 45—35 cm^{-1} lower in wave number than the α,β-unsaturated ketones (1675 cm^{-1}) and IIb (1655 cm^{-1}).

Simple Amine Addition. Amines are known to add most easily to the polarized triple bond in α-acetylenic ketones and secondary amines add exclusively *cis* to the acetylenes to give *trans* products in aprotic solvents,[9]



1) Part LI of this series: T. Sasaki, K. Kanematsu, and A. Kakehi, submitted to *J. Org. Chem.*

2) I. Saikawa, S. Takano, and T. Maeda, *Yakugaku Zasshi*, **87**, 1514 (1967).

3) S. Yoshina, I. Maeba, and K. Asai, *ibid.*, **88**, 984 (1968).

4) T. Sasaki and K. Shoji, *Yuki Gosei Kagaku Kyokai Shi*, **26**, 264 (1968).

5) H. Saikachi and H. Sugimoto, The Annual Meeting of the Pharmaceutical Association of Japan, D-155, Abstract, p. 103 (1966).

6) H. Saikachi, H. Ogawa, N. Shimojo, and K. Uehara, The Annual Meeting of the Pharmaceutical Association of Japan, 6p10-2, Abstract, p. 240 (1969).

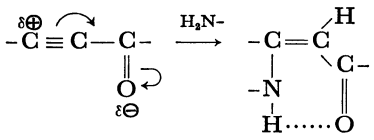
7) E. Winterfeldt, *Angew. Chem. Intern. Ed.*, **6**, 423 (1967); T. F. Rutledge, "Acetylenes and Allenes," Rheinhold, New York (1969), pp. 232—271.

8) T. Sasaki and T. Yoshioka, *Yuki Gosei Kagaku Kyokai Shi*, **28**, 647 (1970).

9) C. H. Mullen and C. J. M. Stirling, *J. Chem. Soc., B*, **1966**, 1217.

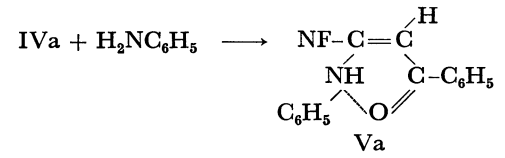
Table 1. 2-(5-Nitro-2-furyl)-1-arylacetylenes (IVa—c)

Compound	Mp °C	Yield %	IR (KBr) cm^{-1} $\nu_{C\equiv C}$	IR (KBr) cm^{-1} ν_{CO}	UV λ_{max}^{EtOH} mμ	UV λ_{max}^{EtOH} (ε)	Found (Calcd) C%	H%	N%
IVa	142—144	80	2280	1625	278	(11500)	64.68	3.09	5.70
					326	(20400)	(64.73	2.93	5.81 for $C_{13}H_7O_4N$)
IVb	146—148	98	2260	1620	280	(15300)	65.63	3.66	5.47
					328	(23800)	(65.88	3.55	5.49 for $C_{14}H_9O_4N$)
IVc	226—227	70	2260	1615	230	(7400)	57.28	2.43	5.87
					300	(14800)	(57.15	2.18	6.06 for $C_{11}H_5O_5N$)
					334	(19500)			

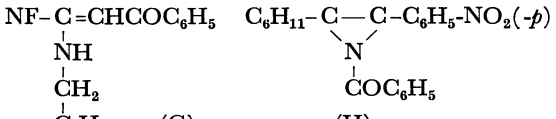


while primary amines do *trans*.[10]

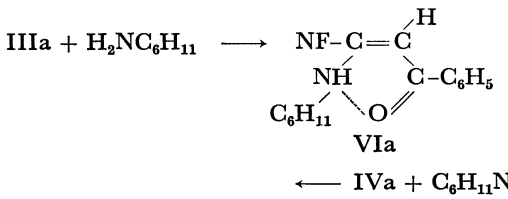
Addition of aniline to IVa was carried out in benzene at room temperature to afford Va; the similarity of its IR and NMR spectral patterns to those of β-benzylamino-5-nitro-2-furfurylidenebenzophenone (G)[8] indicates that both compounds take *cis*-configuration by the *trans*-addition, forming intramolecular hydrogen bonding structure.[10] Since 1-cyclohexyl-2-(*p*-nitrophenyl)-3-benzoylaziridine (H)[11] is prepared from 2,3-dibromo-3-phenyl-*p*-nitropropiophenone and cyclohexylamine, IIIa was treated with cyclohexylamine. However, the product was shown to be not aziridine but β-cyclohexylamino-5-nitro-2-furfurylidenebenzophenone (VIa) by spectral inspection, as in the reaction with aniline.[8] Compound VIa was prepared also by addition of cyclohexylamine to IVa.



Va



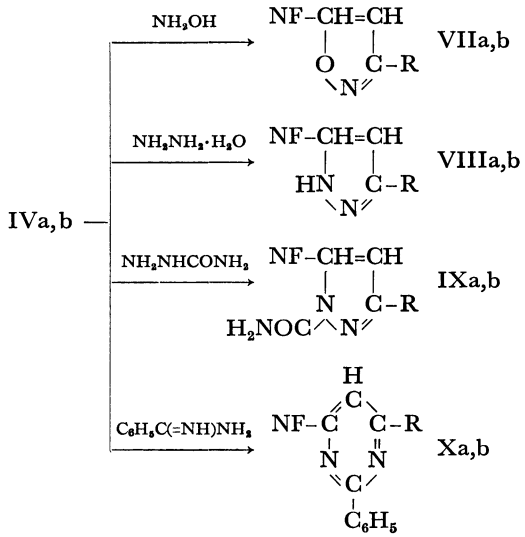
(G) (H)



VIa

← IVa + $C_6H_{11}NH_2$

Heterocyclic Preparation. Acetylenic ketones are good starting materials for synthesizing heterocycles such as isoxazoles and pyrazoles, which have been prepared from hydroxylamine[12] and hydrazine hydrate,[13] respectively. IVa,b were treated with hydroxylamine and hydrazine hydrate to give the expected corresponding isoxazoles (VIIa,b) and pyrazoles (VIIIa, b), respectively. Furthermore, when treated with semicarbazide, IVa,b afforded 1-carbamidopyrazoles (IXa, b) and with benzamidine, IVa,b yielded 2,4,6-trisubstituted pyrimidines (Xa,b), which provide a new method for the preparation of pyrimidines.



The mechanism for the formation of these heterocycles is explained by the initial Michael addition to the triple bond of IV, followed by condensation-cyclization.

1,3-Dipolar Cycloaddition as Dipolarophiles. In spite of abundant information on the cycloaddition of dimethyl acetylenedicarboxylate to several dipoles, there are few reports in literature describing similar reactions of α-acetylenic ketones; they involve the formation of benzo[*b*]furan from 1-phenyl-2-benzoylacetylene and 3,4,5,6-tetrachlorobenzene-2-diazo-1-oxide,[14] of pyrrole from 1-phenyl-2-acylacetylene and *N*-phenyl-*C*-methylsydnone,[15] and of spiroheterocycles from acylacetylene and formamidinium carbodithioates.[16] An example of the Diels-Alder reaction of 1-phenyl-2-acetylacetylene with butadiene has been reported.[17]

10) R. Huisgen, K. Herbig, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966).
11) J. W. Lown, G. Dallas, and T. W. Malony, *Can. J. Chem.*, **47**, 3557 (1969).
12) C. Moureu and M. Brachin, *Bull. Soc. Chim. Fr.*, **31**, 343 (1904).
13) K. Boden and E. R. H. Jones, *J. Chem. Soc.*, **1946**, 953.
14) R. Huisgen, G. Binsch, and H. Koenig, *Chem. Ber.*, **97**, 2884 (1964).
15) R. Huisgen, *Angew. Chem.*, **74**, 29 (1962).
16) H. Behringer and J. Falkenberg, *Tetrahedron Lett.*, **1967**, 1895.
17) D. Nightingale and F. Wadsworth, *J. Amer. Chem. Soc.*, **67**, 416 (1945).

Huisgen[18] and Quilico and Speroni[19] reported isoxazole formation by the 1,3-dipolar cycloaddition of the nitrile oxides with simple acetylenes, but not with α-acetylenic ketones. IVa was therefore treated in benzene at room temperature with benzonitrile oxide prepared '*in situ*' from benzhydroxamoyl chloride and triethylamine. Column chromatography afforded 50% yield of isoxazole (XIa) together with 30% yield of side-produced furoxan. The structure of XIa was tentatively assigned as 3-phenyl-4-benzoyl-5-(5-nitro-2-furyl)-isoxazole in view of the general tendency for the direction of addition occurring at a sterically less hindered position[20] and from consideration of the electron density in IVa.[21] When 5-nitro-2-furocarbonitrile oxide was used instead of benzonitrile oxide under similar conditions, most of IVa was recovered with a small amount of furoxan, but the thermal 1,3-dipolar cycloaddition of IVa,b to the dipole afforded isoxazoles (XIIa,b) with some recovery of IVa,b. For comparison with IVa, the 1,3-dipolar cycloaddition of IIa,b with benzonitrile oxide was carried out, since Quilico[22] reported the synthesis of isoxazoline-4-ketone from α-ethylenic ketones and nitrile oxides:

$$RCH{=}CHCOCH_3 + C_6H_5C{\equiv}N{\rightarrow}O \longrightarrow C_6H_5{-}C(=N{-}O{-}CH(R)){-}CH(COCH_3)$$

IIa was treated with benzonitrile oxide in benzene at room temperature. Chromatography afforded two crystalline products, XIIIa and XIVa, together with furoxan and some recovery of IIa. For the sake of comparison, 5-nitro-2-furfurylideneacetone was treated similarly to give also two crystalline products, XV and XVI, together with furoxan and some recovery of the starting material. From our analyses and Quilicos' results,[22] we tentatively assigned 3-phenyl-4-acetyl-5-(5-nitro-2-furyl)isoxazole for the major product XV and 3-phenyl-4-(5-nitro-2-furyl)-4-acetylisoxazole for the minor product XVI, and similarly, 3-phenyl-4-benzoyl-5-(5-nitro-2-furyl)isoxazole for the major product XIIIa and 3-phenyl-4-(5-nitro-2-furyl)-5-benzoylisoxazole for the minor product XIVa. The IR spectra of XIIIa and XIVa resembled each other as did those of XV and XVI.

$$IVa + C_6H_5C{\equiv}N{\rightarrow}O \longrightarrow C_6H_5{-}C(=N{-}O{-}C(C_6H_5){=}C{-}NF){-}C(=O){-}C_6H_5 \quad (XIa) + C_6H_5{-}C(=N{-}O{-}C(C_6H_5){=}C{-}C_6H_5){=}N{\rightarrow}O$$

18) R. Huisgen, *Angew. Chem.*, **75**, 604 (1963).

19) A. Quilico and G. Speroni, "Five-and Six-membered Compounds," in "The Chemistry of Heterocyclic Compounds," A. Weissberger ed., Vol. 17, Wiley-Interscience, New York (1962), p. 18.

20) R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968).

21) It is reasonably assumed that the same carbon position is initially attacked by the oxygen of the nitrile oxide, where addition of amines takes place:

$$NF{-}C{\equiv}CCOR \quad\quad NF{-}C{\equiv}CCOR$$
$$\uparrow \quad\quad\quad\quad \uparrow$$
$$N \quad\quad\quad\quad O{\leftarrow}N{\equiv}C{-}Ph$$

22) A. Quilico, *Nature*, **166**, 226 (1956); *Gazz. Chim. Ital.*, **80**, 831 (1950); *ibid.*, **85**, 1271 (1955).

$$IVa,b + NF{-}C{\equiv}N{\rightarrow}O \longrightarrow NF{-}C(=N{-}O{-}C(NF){=}C){-}COR \quad (XIIa,b)$$

$$IIa + C_6H_5C{\equiv}N{\rightarrow}O \longrightarrow C_6H_5{-}C(=N{-}O{-}C(NF){=}CH){-}CH(COC_6H_5) \quad (XIIIa)$$

$$+ \quad C_6H_5{-}C(=N{-}O{-}CH(COC_6H_5){=}CH{-}NF){-}CH(NF) \quad (XIVa) \quad + \quad C_6H_5{-}C(=N{-}O{-}C(C_6H_5){=}C{-}C_6H_5){=}N{\rightarrow}O$$

$$NF{-}CH{=}CHCOCH_3 + C_6H_5{-}C{\equiv}N{\rightarrow}O \longrightarrow C_6H_5{-}C(=N{-}O{-}CH(NF){=}CH){-}CH(COCH_3) \quad (XV) + C_6H_5{-}C(=N{-}O{-}CH(NF){=}CH){-}CH(COCH_3) \quad (XVI)$$

For investigating the Diels-Alder reactivity, IVb was treated with butadiene and cyclopentadiene; heating both components in a sealed tube fused with nitrogen at 120°C for 15 hr afforded both intractable tars and with 70% recovery of the starting material in the former reaction.

Another type of 1,3-dipolar cycloaddition reaction has been reported on heterocyclic zwitterions with diethyl acetylenedicarboxylate and ethyl propiolate,[23] and cyanoacetylenes with heterocyclic *N*-ylides and *N*-imines.[24]

Treatment of IVa,b with phenacylpyridinium ylide at room temperature in benzene afforded 73 and 67% yields of XVIIa and XVIIb, respectively. The structural elucidation of XVIIa was carried out in comparison with our previous report.[24] As shown in Fig. 1, quartets centered at 0.40 τ and 1.90 τ are assignable to pyridine ring protons at C_5 and C_8, the lower field shifts being accounted for the anisotropy effect of neighboring carbonyl groups.[24] The higher field shifts of furan ring protons at 3.41 τ and 3.85 τ compared with those of the general nitrofuran derivatives[25] could be explained by the anisotropy effect of the neighboring carbonyls. Thus, the structure of XVIIa was determined as 1-benzoyl-2-(5-nitro-2-furyl)-3-benzoylpyrrocoline.

$$NF{-}C{\equiv}CCOR + \text{(pyridinium ylide)} \quad (IVa, b) \longrightarrow \text{(pyrrocoline)} \quad (XVIIa,b)$$

Experimental

Melting points were measured with a Yanagimoto micro-melting point apparatus and are uncorrected. Microanalyses

23) For a recent review, see V. Boekelheide and N. A. Fedoruk' *J. Org. Chem.*, **33**, 2062 (1969) and refs. therein.

24) T. Sasaki, K. Kanematsu, and Y. Yukimoto, *J. Chem. Soc., C*, **1970**, 481.

25) T. Sasaki, S. Eguchi, and A. Kojima, This Bulletin, **41**, 1568 (1968); *J. Heterocyclic Chem.*, **5**, 243 (1968); T. Sasaki and T. Yoshioka, This Bulletin, **41**, 2212 (1968); *ibid.*, **42**, 258 (1969).

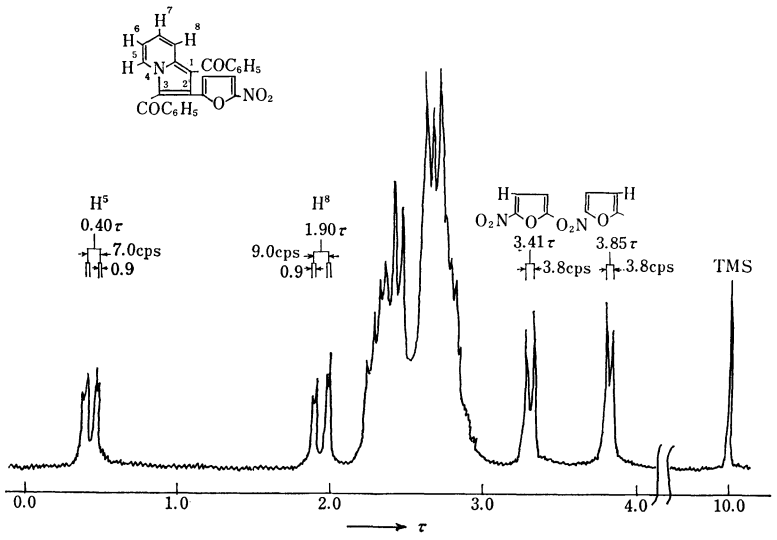


Fig. 1. NMR Spectra of XVIIa.

were performed on a Perkin Elmer 120 elemental analyzer. The NMR spectra were taken with a Jeolco Model JNM-MH-60 NMR spectrometer and with a Varian A-60 recording spectrometer with tetramethylsilane as an internal standard. The chemical shifts are expressed in τ-values. The IR spectra were taken with a JASCO Model IR-S spectrometer and the UV spectra with a JASCO rotary dispersion recorder, Model ORD/UV-5.

Condensation of Nitrofurfural with Aromatic Ketones. Differing from our previous work,[8] concentrated sulfuric acid was used as a condensation reagent as follows: To a solution of 1.4 g (10 mmol) of nitrofurfural and 1.4 g (10 mmol) of *p*-methylacetophenone in 20 m*l* of glacial acetic acid was added 2 m*l* of concentrated sulfuric acid with stirring and the mixture was stirred at 40°C for 1 day. The precipitated crystals were filtered and recrystallized from ethanol to give 1.3 g (45%) of IIb, mp 166—168°C, as pale yellow needles. IR (KBr) cm^{-1}: 1655 (CO) and 1610 (C=C). UV λ_{max}^{EtOH} mμ (ε): 296 (13100) and 348 (23100).

Found: C, 65.14; H, 4.38; N, 5.34%. Calcd for $C_{14}H_{11}O_4N$: C, 65.36; H, 4.31; N, 5.45%.

IIa was prepared similarly in a 50% yield, mp 144°C (lit,[8] 144°C). IIc was prepared by the method of Saikachi and Matsuno.[26]

Preparation of IIIa—c. IIIb,c were prepared similarly to IIIa.[8] IIIb: Yield, 98%, mp 172—174°C. IR (KBr) cm^{-1}: 1680 (CO). UV λ_{max}^{EtOH} mμ (ε): 266 (16100) and 298 (14000).

Found: C, 40.31; H, 2.69; N, 3.18%. Calcd for $C_{14}H_{11}O_4NBr_2$: C, 40.31; H, 2.66; N, 3.36%.

IIIc: Yield, 85%, mp 165—168°C. IR (KBr) cm^{-1}: 1680 (CO). UV λ_{max}^{EtOH} mμ (ε): 242 (13700) an 288 (17800).

Found: C, 33.57; H, 1.81; N, 3.33%. Calcd for $C_{11}H_7O_5NBr_2$: C, 33.70; H, 1.54; N, 3.57%.

Acetylenic Ketones (IVa—c). IVa was prepared as follows: To a stirred solution of 3.0 g (7.5 mmol) of IIIa in 100 m*l* of dry benzene was added a solution of 3 g (30 mmol) of triethylamine in 20 m*l* of dry benzene at room temperature. The mixture was stirred at room temperature for 1 day. After removing 2.5 g of triethylamine hydrobromide, the filtrate was concentrated. The residue was recrystallized from ethanol to give IVa. The yield, spectral data and analyses are given in Table 1. Similarly, IVb and IVc were prepared from IIIb and IIIc after 2 days' strring at room temperature. The results are summarized in Table 1.

Adition of Aniline to IVa. To a stirred solution of 0.4 g (1.65 mmol) of IVa in 50 m*l* of dry benzene was added a solution of 0.2 g (2.2 mmol) of aniline in 20 m*l* of dry benzene at room temperature. After 2 days' stirring at room temperature, the solvent was removed and the residue was recrystallized from ethanol to give 0.5 g (90%) of Va as yellow crystals, mp 141—143°C. IR (KBr) cm^{-1}: 1620 (CO). UV λ_{max}^{EtOH} mμ (ε): 314 (21000) and 390 (15200). NMR ($CDCl_3$)τ: −1.2 (NH), 2.0—3.0 (m, 12H, phenyl and nitrofuran ring protons), and 3.65 (s, 1H, =CH–).

Found: C, 67.85; H, 4.26; N, 8.15%. Calcd for $C_{19}H_{14}O_4N_2$: C, 68.25 H, 4.22; N, 8.38%.

β-Cyclohexylamino-5-nitro-2-furfurylidenebenzophenone (VIa). To a stirred and ice-cooled solution of 1 g (2.5 mmol) of IIIa in 50 m*l* of dry benzene was added a solution of 1.5 g (15 mmol) of cyclohexylamine in 20 m*l* of dry benzene. The solution was stirred at room temperature overnight. The solvent was removed and the residue was chromatographed on a silica-gel column using chloroform as an eluent. The first fraction afforded 0.4 g (47%) of VIa, mp 96—97°C, as red crystals (ethanol-petroleum ether). IR (KBr) cm^{-1}: 1610 (CO). UV λ_{max}^{EtOH} mμ (ε): 306 (14000) and 400 (12600). NMR ($CDCl_3$)τ: −1.3 (NH), 2.0—3.0 (m, 7H, phenyl and nitrofuran ring protons), 3.88 (s, 1H, =CH–), and 7.9—8.8 (m, 11H, cyclohexane ring protons).

Found: C, 67.39; H, 5.98; N, 8.06%. Calcd for $C_{19}H_{20}O_4N_2$: C, 67.04; H, 5.92; N, 8.23%.

The same compound was prepared quantitatively from IVa and cyclohexylamine by the same procedure as in the addition of aniline to IVa.

3-Phenyl-5-(5-nitro-2-furyl)isoxazole (VIIa). A mixture of 0.25 g (1 mmol) of IVa, 0.2 g (3 mmol) of hydroxylamine hydrochloride and 20 m*l* of ethanol was refluxed for 12 hr. After cooling, the resulting precipitates were filtered and recrystallized from ethanol to give 0.1 g (40%) of VIIa, mp 198—200°C, which showed mixed melting point depression with 3-(5-nitro-2-furyl)-5-phenylisoxazole.[27] IR (KBr) cm^{-1}: 1620 (C=N). UV λ_{max}^{EtOH} mμ (ε): 230 (18600) and 330 (14200). NMR ($CDCl_3$) τ: 2.0—2.8 (m, 7H, phenyl and nitrofuran ring protons) and 2.86 (s, 1H, isoxazole C_4-H).

Found: C, 61.18; H, 3.33; N, 11.02%. Calcd for $C_{13}H_8O_4N_2$: C, 60.94; H, 3.15; N, 10.93%.

26) H. Saikachi and J. Matsuno, *Yakugaku Zasshi*, **89**, 1622 (1969),

27) T. Sasaki and T. Yoshioka, This Bulletin, **40**, 2604 (1967).

3-(p-Methylphenyl)-5-(5-nitro-2-furyl)isoxazole (VIIb). Under similar treatment, IVb afforded 35% yield of VIIb, mp 205—207°C (ethanol). IR (KBr) cm^{-1}: 1615 (C=N). UV λ_{max}^{EtOH} mμ (ε): 232 (19000) and 332 (15000). NMR ($CDCl_3$) τ: 2.1—2.8 (m, 6H, phenyl and nitrofuran ring protons), 2.90 (s, 1H, isoxazole C_4-H), and 7.57 (s, CH_3).

Found: C, 61.76; H, 3.74; 10.14%. Calcd for $C_{14}H_{10}O_4N_2$: C, 62.22; H, 3.73; N, 10.37%.

5-(5-Nitro-2-furyl)-3-phenyl-1H,2-pyrazole (VIIIa). To a stirred solution of 0.3 g (1.25 mmol) of IVa in a mixture of 20 m*l* of benzene and 20 m*l* of ethanol was added a solution of 0.15 g (4 mmol) of 80% hydrazine hydrate in 10 m*l* of ethanol under ice-cooling. The mixture was stirred at room temperature for 2 days. The solvents were removed and the residue was treated with 20 m*l* of water. The insoluble part was filtered and recrystallized from benzene-ethanol to give 95% yield of VIIIa, mp 227°C (lit,[8] mp 225—228°C).

5-(5-Nitro-2-furyl)-3-p-methylphenyl-1H,2-pyrazole (VIIIb). Similar treatment afforded 97% yield of VIIIb, mp 241—243°C (ethanol-benzene). IR (KBr) cm^{-1}: 3180 (NH). NMR (DMSO-d_6) τ: −2.8 (NH), 2.70 (s, 1H, pyrazole C_4-H), and 7.65 (s, CH_3).

Found: C, 62.41; H, 4.28; N, 15.53%. Calcd for $C_{14}H_{11}O_3N_3$: C, 62.45; H, 4.12; N, 15.61%.

1-Carbamido-3-phenyl-5-(5-nitro-2-furyl)pyrazole (IXa). A mixture of 0.4 g (1.65 mmol) of IVa, 0.3 g (2.7 mmol) of semicarbazide hydrochloride and 25 m*l* of ethanol was refluxed for 11 hr. The solvent was removed and the residue was treated with 30 m*l* of water. The insoluble part was filtered and recrystallized from ethanol-benzene to give 0.3 g (54%) of IXa, mp 215—216°C, as pale yellow needles. IR (KBr) cm^{-1}: 3380, 3250 (NH) and 1660 (CO). NMR (DMSO-d_6) τ: 0.20 (broad s, 1H, HCl), 2.1—2.7 m, 7H, phenyl and nitrofuran ring protons, 2.66 (s, 1H, pyrazole C_4-H), and 3.4 (broad, 2H, NH_2, disappeared on deuteration).

Found: C, 50.07; H, 3.35; N, 17.02%. Calcd for $C_{14}H_9O_4N_4HCl$: C, 50.39; H, 3.02; N, 16.79%.

1-Carbamido-3-p-methylphenyl-5-(5-nitro-2-furyl)pyrazole (IXb). Similar treatment afforded 60% yield of IXb, mp 224—228C°. IR (KBr) cm^{-1}: 3400, 3250 (NH), and 1660 (CO).

Found: C, 52.00; H, 3.86; N, 16.53%. Calcd for $C_{15}H_{12}O_4N_4HCl$: C, 51.66; H, 3.76; N, 16.07%.

2-Phenyl-4-phenyl-6-(5-nitro-2-furyl)pyrimidine (Xa). A mixture of 0.4 g (1.6 mmol) of IVa, 0.3 g (2 mmol) of benzamidine hydrochloride and 20 m*l* of ethanol was refluxed for 12 hr. After cooling, the resulting precipitates were filtered and recrystallized from ethanol-benzene to give 0.13 g (25%) of Xa, mp 213—215°C, as colorless needles. UV λ_{max}^{EtOH} mμ (ε): 260 (32000) and 328 (17000). NMR ($CDCl_3$) τ: 1.2—1.7 (m, 4H, phenyl protons), 1.97 (s, 1H, pyrimidine C_5-H), and 2.3—2.6 (m, 8H, phenyl and nitrofuran ring protons).

Found: C, 69.91; H, 3.94; N, 12.28%. Calcd for $C_{20}H_{13}O_3N_3$: C, 69.96; H, 3.82; N, 12.24%.

From the filtrate, 0.16 g (40%) of IVa was recovered by column chromatography on a silica-gel using chloroform as an eluent.

2-Phenyl-4-p-methylphenyl-6-(5-nitro-2-furyl)pyrimidine (Xb). Similar treatment of IVb and amidine afforded 20% yield of Xb, mp 220—223°C (ethanol-benzene). UV λ_{max}^{EtOH} mμ (ε): 264 (37000) and 330 (18400). NMR ($CDCl_3$) τ: 1.3—1.9 (m, 4H, phenyl protons), 2.08 (s, 1H, pyrimidine C_5-H), 2.4—2.7 (m, 7H, phenyl and nitrofuran protons), and 7.55 (s, CH_3).

Found: C, 70.56; H, 4.36; N, 11.71%. Calcd for $C_{21}H_{15}O_3N_3$: C, 70.58; H, 4.23; N, 11.76%.

3-Phenyl-4-benzoyl-5-(5-nitro-2-furyl)isoxazole (XIa). To a stirred solution of 0.6 g (2.5 mmol) of IVa and 0.4 g (2.6 mmol) of benzhydroxamoyl chloride in 50 m*l* of dry benzene was added a solution of 0.9 g (9 mmol) of triethylamine in 20 m*l* of dry benzene under ice-cooling. After stirring for 1 day at room temperature, the reaction mixture was filtered and the solvent was removed from the filtrate. The residue was chromatographed on a silica-gel column using benzene as an eluent. The first fraction afforded 0.1 g (30%) of furoxan, mp 115—116°C.[27] From the second fraction a small amount of oil was obtained, which was discarded without further investigation. The third fraction afforded the main product, 0.45 g (50%) of XIa, mp 135—138°C (ethanol). IR (KBr) cm^{-1}: 1655 (CO). UV λ_{max}^{EtOH} mμ (ε): 228 (20100), 250 (16200), and 328 (14000).

Found: C, 66.48; H, 3.48; N, 7.59%. Calcd for $C_{20}H_{12}O_5N_2$: C, 66.66; H, 3.36; N, 7.78%.

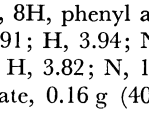
Thermal 1,3-Dipolar Cycloaddition of IVa,b to 5-Nitro-2-furocarbonitrile Oxide. A solution of 0.4 g (1.65 mmol) of IVa and 0.3 g (1.6 mmol) of 5-nitro-2-furohydroxamoyl chloride in 20 m*l* of toluene was refluxed for 20 hr until the hydrogen chloride gas evolution had completely ceased. After removing the solvent, the reside was chromatographed on a silica-gel column using chloroform as an eluent. The first fraction afforded 0.1 g (25%) of recovered IVa and the second fraction yielded 0.23 g (30%) of 3,5-di(5-nitro-2-furyl)-4-benzoylisoxazole (XIIa), mp 193—195°, (ethanol-benzene). IR (KBr)cm^{-1}: 1660 (CO). UV λ_{max}^{EtOH} mμ (ε): 250 (14000) and 322 (19000).

Found: C, 55.28; H, 2.44; N, 11.13%. Calcd for $C_{18}H_9O_7N_3$: C, 55.53; H, 2.39; N, 11.08%.

Similar treatment of IVb afforded 30% recovery of IVb and 20% yield of 3,5-di(5-nitro-2-furyl)-4-methylbenzoylisoxazole (XIIb), mp 191—193°C (ethanol-benzene). IR (KBr) cm^{-1}: 1655 (CO). UV λ_{max}^{EtOH} mμ (ε): 256 (16000) and 324 (19800).

Found: C, 55.90; H, 2.86; N, 10.15%. Calcd for $C_{19}H_{11}O_8N_3$: C, 55.75; H, 2.71; N, 10.27%.

1,3-Dipolar Cycloaddition of IIa to Benzonitrile Oxide. To a stirred solution of 0.55 g (2.3 mmol) of IIa and 0.4 g (2.6 mmol) of benzhydroxamoyl chloride in 40 m*l* of dry benzene was added a solution of 0.5 g (5 mmol) of triethylamine in 20 m*l* of dry benzene under ice-cooling. The mixture was stirred at room temperature for 1 day. After removing insoluble triethylamine hydrochloride by filtration, the solvent was removed from the filtrate. The residue was chromatographed on a silica-gel column using benzene as an eluent. The first fraction afforded 0.03 g (10%) of furoxan, mp 115°C.[27] From the following fractions, 0.03 g (4%) of XIVa, mp 118—120°C, 0.2 g (40%) of recovered IIa and 0.4 g (40%) of XIIIa, mp 196—197°C (ethanol-benzene) were obtained successively. The IR spectrum of XIVa was similar to that of XIIIa.

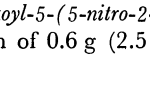
XIIIa: IR (KBr) cm^{-1}: 1675 (CO). UV λ_{max}^{EtOH} mμ (ε): 244 (21400) and 298 (10000). NMR ($CDCl_3$) τ: 1.8—2.7 (m, 11H, phenyl and nitrofuran ring[28] protons), 3.20 (d, 1H, J=4 Hz, ) 4.10 (d, 1H, J=6 Hz, isoxazole C_5-H), and 4.28 (d, 1H, J=6 Hz, isoxazole C_4-H).

Found: C, 66.47; H, 4.03; N, 7.57%. Calcd for $C_{20}H_{14}O_5N_3$: C, 66.29 H, 3.89; N, 7.73%.

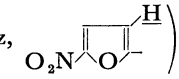
XIVa:

Found: C, 66.35; H, 3.99; N, 7.65%. Calcd for $C_{20}H_{14}O_5N_2$: C, 66.29; H, 3.89; N, 7.73%.

1,3-Dipolar Cycloaddition of 5-Nitro-2-furfurylideneacetone to Benzonitrile Oxide. From a similar treatment of 5-nitro-

28) One of two: 

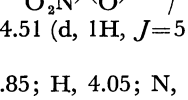
2-furfurylideneacetone[8] and benzonitrile oxide, 10% of furoxan, 10% of XVI, mp 60—62°C, and 40% of XV, mp 108—109°C (ethanol) were successively obtained. The IR spectrum of XV was similar to that of XVI.

XV: IR (KBr) cm^{-1}: 1705 (CO). UV λ_{max}^{EtOH} mμ (ε): 255 (15500) and 300 (15500). NMR (DMSO-d_6) τ: 2.2—2.6 (m, 6H, phenyl and nitrofuran[28] ring protons), 2.90 (d, 1H, J=4 Hz, ), 3.76 (d, 1H, J=5 Hz, isoxazoline C_5-H), 4.51 (d, 1H, J=5 Hz, isoxazoline C_4-H), and 7.66 (s, CH_3).

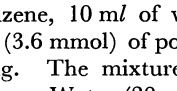
Found: C, 59.85; H, 4.05; N, 9.29%. Calcd for $C_{15}H_{12}O_5N_2$: C, 60.00; H, 4.03; N, 9.33%.

XVI:

Found: C, 60.15; H, 3.95; N, 9.45%. Calcd for $C_{15}H_{12}O_5N_2$: C, 6.00; H, 4.05; N, 9.33%.

1-Benzoyl-2-(5-nitro-2-furyl)-3-benzoylpyrrocoline (XVIIa). To a stirred solution of 0.3 g (1.25 mmol) of IVa and 1 g (3.6 mmol) of phenacyl pyridinium bromide[29] in a mixture of 30 m*l* of benzene, 10 m*l* of water and 10 m*l* of ethanol was added 0.5 g (3.6 mmol) of powdered potassium carbonate under ice-cooling. The mixture was stirred at room temperature for 2 days. Water (20 m*l*) was added to the mixture and the mixture was extracted with benzene (3×50 m*l*). The benzene extracts were dried over sodium sulfate and benzene was removed from the extracts. The residue was chromatographed on a silica-gel column using chloroform as an eluent to give 0.4 g (73%) of XVIIa as yellow needles, mp 212—214°C (ethanol-benzene). IR (KBr) cm^{-1}: 1640 (CO). UV λ_{max}^{EtOH} mμ (ε): 230 (24000) and 340 (18000). NMR ($CDCl_3$) τ: 0.40 (dd, 1H, J=0.9, 7.0 Hz, C_5-H), 1.9 (dd, 1H, J=0.9, 9.0 Hz, C_8-H), 2.3—3.0 (m, 12H, phenyl (10H) and pyridine (2H) ring protons), 3.35 (d, 1H, J=4 Hz, ) and 3.85 (d, 1H, J=4 Hz,).

Found: C, 71.74; H, 3.85; N, 6.24%. Calcd for $C_{26}H_{16}O_5N_2$: C, 71.56; H, 3.85; N, 6.42%.

1-p-Methylbenzoyl-2-(5-nitro-2-furyl)-3-benzoylpyrrocoline (XVIIb). Similar treatment afforded 70% yield of XVIIb as yellow needles, mp 195—197°C (ethanol-benzene). IR (KBr) cm^{-1}: 1640 (CO). UV λ_{max}^{EtOH} mμ (ε): 235 (23800) and 338 (20000). NMR ($CDCl_3$) τ: 0.42 (dd, 1H, J=0.9, 7.0 Hz, C_5-H), 2.02 (dd, 1H, J=0.9, 9 Hz, C_8-H), 2.4—3.1 (m, 11H, phenyl (9H) and pyridine (2H) protons), 3.35 (d, 1H, J=3.8 Hz, ), 3.80 (d, 1H, J=3.8 Hz,), and 7.73 (s, CH_3).

Found: C, 72.25; H, 4.13; N, 6.13%. Calcd for $C_{27}H_{18}O_5N_2$: C, 71.99; H, 4.03; N, 6.22%.

29) F. Kröhnke, *Chem. Ber.*, **68**, 1177 (1935).