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Studies on Heterocyclic Compounds. XII.[1] Synthesis of Furo[2,3-*d*]-pyridazine Derivatives. (3). Synthesis of 2-Methyl-8-chloro-6-substituted-*sym*-triazolo[2,1-*f*]furo[2,3-*d*]-pyridazine Derivatives

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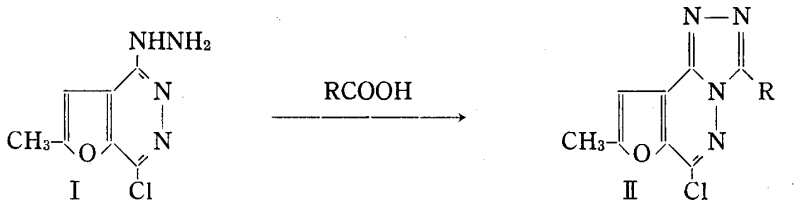
The synthesis of *sym*-triazolo[4,3-*b*]pyridazine derivatives as useful antitumor agent were recently reported by Castle, *et al.*[3,4] This report prompted us to investigate systematic synthesis of substituted-*sym*-triazolo[2,1-*f*]furo[2,3-*d*]pyridazines (II) containing alkyl, aryl and heteryl substituents at position 6, which appeared to have some biological activities.

Many of the derivatives of triazolo[3,4-*a*]phthalazine[5–7] and pyrido[3,2-*d*]-*sym*-triazolo-[4,3-*b*]pyridazine[8–10] have been reported, but in the triazolo[2,1-*f*]furo[2,3-*d*]pyridazine ring system only two compounds have been described by Robba, *et al.*,[11] namely *sym*-triazolo-[2,1-*f*]furo[2,3-*d*]pyridazine and 6-methyl-*sym*-triazolo[2,1-*f*]furo[2,3-*d*]pyridazine.

For the synthesis of II, 2-methyl-7-chloro-4-hydrazinofuro[2,3-*d*]pyridazine(I)[12] served as the starting material.

Compound II was prepared by cyclization of I with the appropriate acid according to a reported method.[9]



I II

R=alkyl, aryl, heteryl

Chart 1

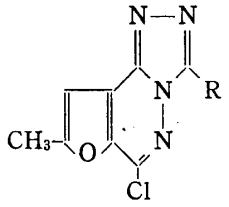
Reaction of I with excess of the aliphatic acids under heating in a water bath for 1—2 hours gave 6-alkyl compounds in good yield (70—80%). It was convenient in the case of the aliphatic acids to use excess of the acid as a solvent.

Products of this type are described in Table I.

Reaction of I with oxalic acid gave IV instead of the expected product III. We considered that decarboxylation of 6-carboxyl group of III occurred to give IV. Compound (IV) was identical with the product which was obtained by the reaction of I with HCOOH (Chart 2).

1) Part XI: S. Yoshina and I. Maeba, *Chem. Pharm. Bull.* (Tokyo), **18**, 379 (1970).
2) Location: *Tenpaku-cho, Showa-ku, Nagoya.*
3) T. Kuraishi and R.N. Castle, *J. Heterocyclic Chem.*, **1**, 42 (1966).
4) H. Murakami and R.N. Castle, *J. Heterocyclic Chem.*, **4**, 555 (1967).
5) M. Hartmann and J. Druey, U.S. Patent 2484029 (1949) [*C.A.*, **44**, 4046 (1950)].
6) J. Druey and B.H. Ringier, *Helv. Chim. Acta.*, **34**, 195 (1951).
7) G.A. Reynolds, J.A. VanAllan and J.F. Tinker, *J. Org. Chem.*, **24**, 1205 (1959).
8) C. Farbwerke, Ger. Patent 951993 (1956) [*C.A.*, **53**, 5298 (1959)].
9) T. Otaka and Y. Nitta, *Chem. Pharm. Bull.* (Tokyo), **13**, 586 (1965).
10) B. Stanovnik, A. Krbavcic and M. Tisler, *J. Org. Chem.*, **32(4)**, 1139 (1967).
11) M. Robba and M.C. Zaluski, *Compt. Rend.*, **266**, 31 (1968).
12) S. Yoshina, I. Maeba and K. Hirano, *Chem. Pharm. Bull.* (Tokyo), **17**, 2158 (1969).

Table I.



R	mp (°C)	Yield	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
H–	230—231	74	$C_8H_5ON_4Cl$	46.06	2.42	26.86	45.91	2.63	26.57
CH_3–	219	68	$C_9H_7ON_4Cl$	48.55	3.17	25.17	48.92	3.10	25.44
CH_3CH_2–	190—191	81	$C_{10}H_9ON_4Cl$	50.75	3.83	23.67	51.06	3.48	23.72
$CH_3(CH_2)_2$–	157—158	69	$C_{11}H_{11}ON_4Cl$	52.07	4.42	22.35	52.31	4.25	22.63
$CH_3(CH_2)_3$–	131	84	$C_{12}H_{13}ON_4Cl$	54.45	4.95	21.16	54.87	4.57	21.39
$CH_3(CH_2)_4$–	135	81	$C_{13}H_{15}ON_4Cl$	56.02	5.42	20.01	55.73	5.34	20.21
$CH_3(CH_2)_5$–	122—123	73	$C_{14}H_{17}ON_4Cl$	57.44	5.85	19.14	57.22	5.67	19.28
$CH_3(CH_2)_6$–	124	78	$C_{15}H_{19}ON_4Cl$	58.73	6.24	18.26	58.74	6.08	18.43
$CH_3(CH_2)_7$–	116—117	80	$C_{16}H_{21}ON_4Cl$	59.90	6.60	17.46	59.63	6.47	17.75
$CH_3(CH_2)_8$–	107—109	72	$C_{17}H_{23}ON_4Cl$	60.98	6.92	16.73	61.16	6.79	17.04
$-CH_2OH$	232—233	66	$C_9H_7O_2N_4Cl$	45.30	2.96	23.48	45.58	3.09	23.72
$-CH_2CN$	205—206	71	$C_{10}H_6ON_5Cl$	48.50	2.44	28.27	48.79	2.67	28.64
$-CH_2Cl$	218	57	$C_9H_6ON_4Cl_2$	42.05	2.35	21.79	42.36	2.51	21.53
$-CHCl_2$	224—225	62	$C_9H_5ON_4Cl_3$	37.08	1.73	19.23	37.38	1.53	19.35
$-CCl_3$	175	59	$C_9H_4ON_4Cl_4$	33.16	1.24	17.19	32.81	1.58	17.36
$-CH_2Br$	207—208	41	$C_9H_6ON_4BrCl$	35.85	2.01	18.58	35.64	1.84	18.42

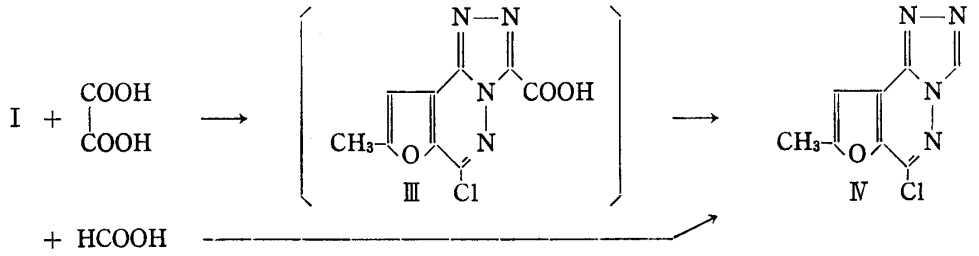


Chart 2

6-Aryl and heteryl compounds were obtained when I was heated with 1.5 moles of the appropriate acids at 180—200° for 10 minutes.

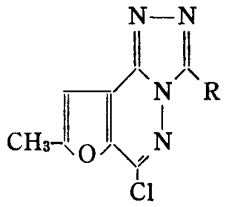
The lower temperature and shorter time needed for this reaction to occur resulted in less decomposition and in increased yield; occasionally, the presence of polymeric-type material in the crude reaction mixtures made their purification to analytical standards somewhat difficult, but their purification could be achieved by repeated recrystallizations from a suitable solvent.

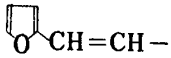
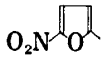
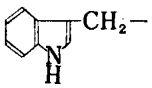
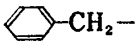
Products of this type are described in Table II.

Treatment of I with 2-furylacrylic acid gave 2-methyl-8-chloro-6-(2-furylvinyl)-*sym*-triazolo[2,1-*f*]furo[2,3-*d*]pyridazine(V) mp 240—241°. However, 2-methyl-8-chloro-6-[2-(5-nitro-2-furyl)vinyl]-*sym*-triazolo[2,1-*f*]furo[2,3-*d*]pyridazine(VI) was not obtained when I was allowed to react with 5-nitro-2-furylacrylic acid. Compound(VI) was finally synthesized by a Wittig reaction as shown in Chart 3.

Reaction of I with bromoacetic acid gave VII. Condensation of halide(VII) with triphenylphosphine took place smoothly in refluxing benzene, giving VIII in yield 63%, mp 256°.

TABLE II.



R	mp (°C)	Yield	Recryst. solv.	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
	262—263	32	MeOH	$C_{12}H_7O_2N_4Cl$	52.48	2.57	20.40	52.36	2.41	20.68
	240—241	18	MeOH	$C_{14}H_9O_2N_4Cl$	55.92	3.02	18.63	56.37	2.96	18.49
	259—260	28	MeOH	$C_{12}H_6O_2N_4BrCl$	40.77	1.71	15.85	41.27	1.59	15.63
	251—252	13	MeOH	$C_{12}H_6O_4N_5Cl$	45.09	1.89	21.91	44.74	2.03	21.63
	228—229	46	AcOEt	$C_{12}H_7ON_4SCl$	49.58	2.43	19.27	49.50	2.28	18.94
	246—247	35	AcOEt	$C_{13}H_8ON_5Cl$	54.65	2.82	24.51	54.83	3.09	24.72
	243—244	29	AcOEt	$C_{17}H_{10}ON_5Cl$	60.82	3.00	20.86	61.17	2.85	20.59
	246—247	54	MeOH	$C_{17}H_{12}ON_5Cl$	60.45	3.58	20.73	60.74	3.26	21.08
	224	57	MeOH	$C_{14}H_9ON_4Cl$	59.06	3.19	19.68	58.85	3.37	19.41
	183—184	61	MeOH	$C_{15}H_{11}ON_4Cl$	60.31	3.71	18.75	60.62	4.08	18.97

Sodium hydride was added in small portions to a solution of VIII and 5-nitro-2-furaldehyde in anhydrous MeOH with stirring at room temperature. The precipitate was collected by filtration and recrystallized from AcOEt to yield VI, mp 287—289°.

Moreover, reaction of VIII with furfural gave the same product which was obtained by the reaction of I with 2-furylacrylic acid.

The products which was obtained by Wittig reaction are described in Table III.

We considered that 6-methyl group of IX attached to a π-deficient nucleus is readily condenced with aldehyde.

Treatment of IX with 5-nitro-2-furaldehyde in the presence of acetic anhydride or mixture of acetic anhydride and acetic acid in the ratio 10:1 as condensing agents led to recovery of

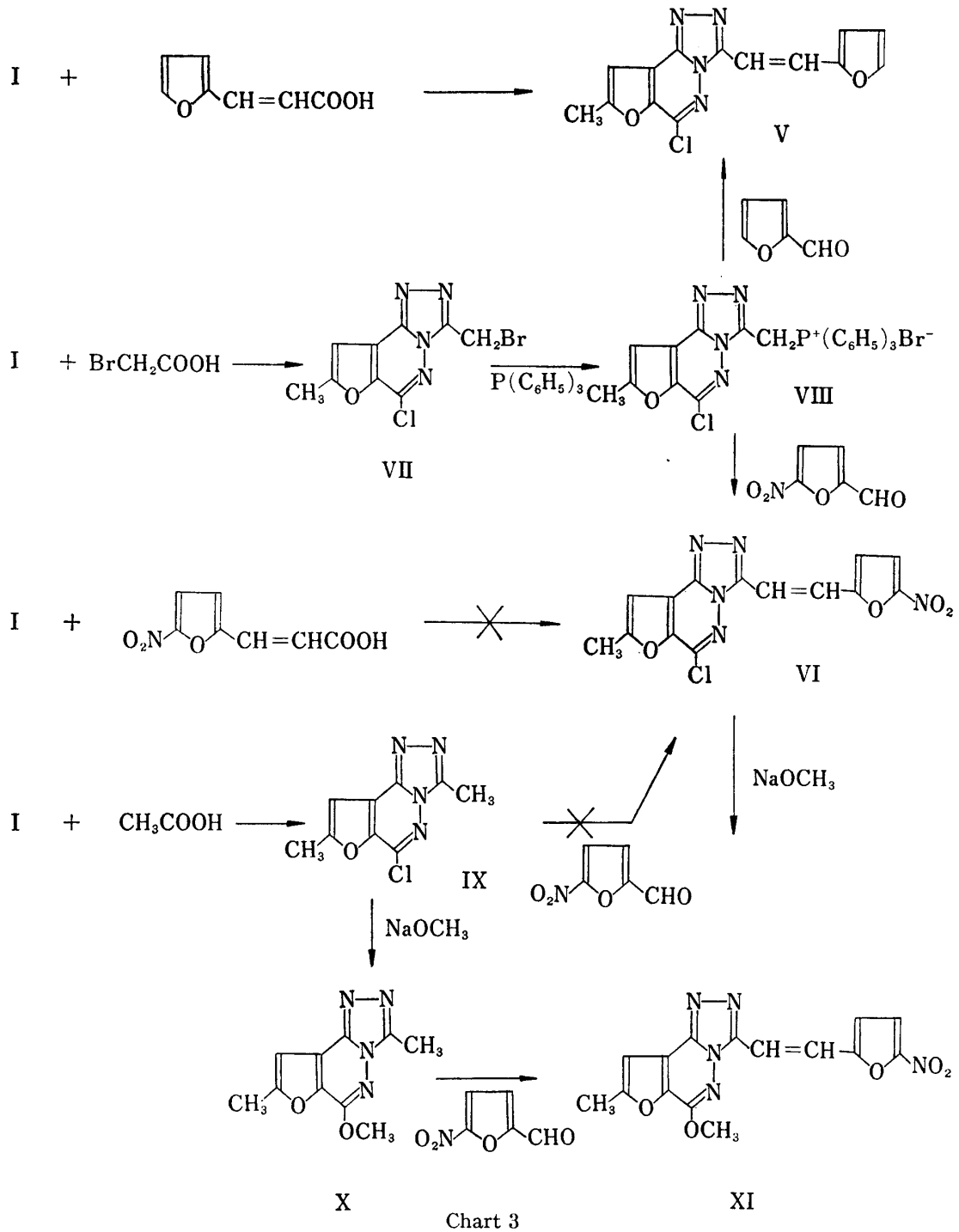


Chart 3

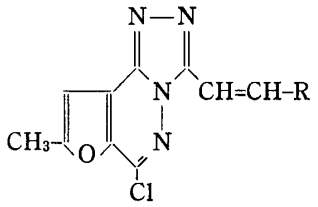
starting material. Albert, *et al.*[13] reported that π-deficient N-heteroaromatics with an α- or γ-hydroxy-group as well as a γ- or α- methyl-group will not condence with aldehydes, but the condensation can be carried out if the hydroxy- is changed to methoxy- through a chloro-group.

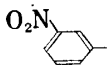
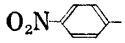
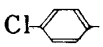
So that, we synthesized 2,6-dimethyl-8-methoxy-*sym*-triazolo[2,1-*f*]furo[2,3-*d*]pyridazine (X) by reaction of IX with $NaOCH_3$.

Condensation of X with 5-nitro-2-furaldehyde proceeded smoothly in refluxing mixture of acetic anhydride and acetic acid in the ratio 10:1 to yield 2-methyl-8-methoxy-6-[2-(5-nitro-2-furyl)vinyl]-*sym*-triazolo[2,1-*f*]furo[2,3-*d*]pyridazine (XI).

13) A. Albert, "Heterocyclic Chemistry an Introduction," Athlone Press, University of London, 1959.

TABLE III.



R	mp (°C)	Yield	Recryst. solv.	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
	287—289	48	AcOEt	$C_{14}H_8O_4N_5Cl$	48.64	2.33	20.26	48.75	2.53	20.04
	245—246	62	MeOH	$C_{14}H_8O_2N_4BrCl$	44.30	2.12	14.76	44.57	2.36	14.54
	230—231	55	AcOEt	$C_{14}H_9ON_4SCl$	53.08	2.86	17.69	52.84	3.01	17.43
	260—262	67	MeOH	$C_{15}H_{10}ON_5Cl$	57.80	3.23	22.47	57.69	2.98	22.62
	205—206	58	MeOH	$C_{15}H_{10}ON_5Cl$	57.80	3.23	22.47	57.93	2.85	22.31
	213—214	61	MeOH	$C_{15}H_{10}ON_5Cl$	57.80	3.23	22.47	58.11	3.17	22.59
	234—235	70	MeOH	$C_{16}H_{11}ON_4Cl$	61.84	3.57	18.08	61.64	3.73	17.88
	235—237	50	AcOEt	$C_{16}H_{10}O_3N_5Cl$	54.02	2.83	19.69	54.42	2.79	19.82
	261—262	59	AcOEt	$C_{16}H_{10}O_3N_5Cl$	54.02	2.83	19.69	54.24	2.48	19.83
	292—293	60	AcOEt	$C_{16}H_{10}O_3N_5Cl$	54.02	2.83	19.69	53.78	2.52	19.46
	213	51	AcOEt	$C_{16}H_{10}ON_4Cl_2$	55.67	2.92	16.23	55.71	2.83	15.95
	254—257	53	AcOEt	$C_{16}H_{10}ON_4Cl_2$	55.67	2.92	16.23	55.92	3.17	16.33
	217—219	57	AcOEt	$C_{16}H_{10}ON_4Cl_2$	55.67	2.92	16.23	55.84	3.06	16.14

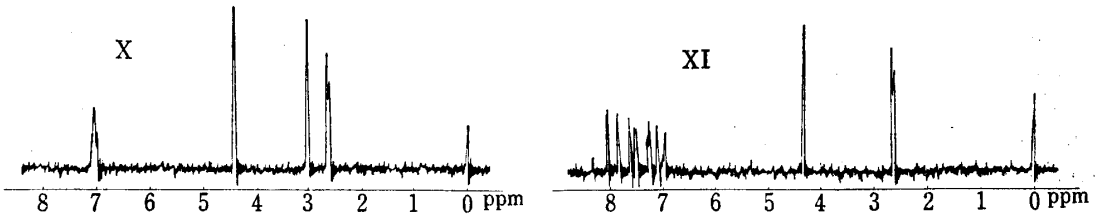


Fig. 1. NMR Spectra of X and XI in CF_3COOH

On comparison of the nuclear magnetic resonance NMR spectra (Fig. 1) of X with XI, the former showed the signals at 2.72 ppm (C_2–CH_3, d., J=1.5 cps) and 3.05 ppm (C_6–CH_3, s.), while the C_6–CH_3 signal disappeared with the latter. Compound (XI) was identical with the product which was obtained by the reaction of VI with $NaOCH_3$.

Experimental[14]

2-Methyl-8-chloro-6-alkyl-*sym*-triazolo[2,1-*f*]furo[2,3-*d*]pyridazines——2-Methyl-7-chloro-4-hydrazinofuro[2,3-*d*]pyridazine (I) (0.01 mole) was heated in water bath with the aliphatic acids (0.1 mole) for 1—2 hr. The reaction mixture was poured into ice water. The precipitate was filtered off, purified by crystallization from MeOH. These products are described in Table I.

2-Methyl-8-chloro-6-aryl(or heteryl-) *sym*-triazolo[2,1-*f*]furo[2,3-*d*]pyridazines——Compound (I) (0.01 mole) was heated with aromatic or heterocyclic acids (0.015 mole) at 180—200° for 10 min. The dark red residue was purified by repeated crystallization from a suitable solvent and by treatment with decolorizing carbon. These products are described in Table II.

Phosphonium Salt (VIII)——A mixture of 2-methyl-8-chloro-6-bromomethyl-*sym*-triazolo[2,1-*f*]furo[2,3-*d*]pyridazine (VII) 3.0 g (0.01 mole), triphenylphosphine 3.1 g (0.012 mole) and 30 ml of anhydrous benzene refluxed for 5 hr. After cooling, the white crystalling precipitate was isolated, washed with 10 ml of benzene and dried. In this manner, 3.6 g (63%) of phosphonium salt (VIII) was obtained, mp 256°. *Anal.* Calcd. for $C_{27}H_{21}ON_4BrClP$: C, 57.52; H, 3.75; N, 9.94. Found: C, 57.39; H, 3.86; N, 10.15.

2-Methyl-8-chloro-6-(2-furylvinyl)-*sym*-triazolo[2,1-*f*]furo[2,3-*d*]pyridazine (V)——A) Compound (I) (2.0 g) and furylacrylic acid (2.0 g) were heated at 180—190° for 10 min. After cooling, brownish residue was purified by repeated crystallization from AcOEt to give pale yellow prisms (V) mp 240—241°.

B) Sodium hydride (0.17) was added in small portions to a solution of phosphonium salt (VIII) (1.9 g) and furfural (0.4 g) in anhydrous MeOH with stirring at room temperature. The resulting crystalline substance was collected by filtration.

Recrystallization from AcOEt gave pale yellow prisms (V) mp 240—241°. Identity was confirmed by comparing IR spectra and mixed melting point.

2-Methyl-8-chloro-6-[2-(5-nitro-2-furyl)vinyl]-*sym*-triazolo[2,1-*f*]furo[2,3-*d*]pyridazine (VI)——Compound (VI) was made as described above with V-B.

2,6-Dimethyl-8-methoxy-*sym*-triazolo[2,1-*f*]furo[2,3-*d*]pyridazine (X)——Compound (IX) (2.2 g) was added in small portions to a solution of Na (0.23 g) in anhydrous MeOH (30 ml) with stirring at room temperature. Stirring was continued for an additional 30 min. The reaction mixture was filtered off, concentrated and cooled to give crystalline precipitate, which on recrystallization from MeOH gave (X) 1.7 g, mp 207°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_4$: C, 55.04; H, 4.62; N, 25.67. Found: C, 54.83; H, 4.75; N, 25.49.

2-Methyl-8-methoxy-6-[2-(5-nitro-2-furyl)vinyl]-*sym*-triazolo[2,1-*f*]furo[2,3-*d*]pyridazine (XI)——A) A mixture of X (0.5 g), 5-nitro-2-furaldehyde (0.4 g) and 11 ml of acetic anhydride and acetic acid in the ratio 10:1 was refluxed for two hours.

After cooling, the yellow crystalling precipitate was isolated and recrystallized from DMF to give (XI) 0.4 g, mp 244—245°. *Anal.* Calcd. for $C_{15}H_{11}O_4N_5$: C, 55.39; H, 3.41; N, 21.53. Found: C, 55.74; H, 3.58; N, 21.41.

B) Compound (VI) (0.1 g) was dissolved in MeOH (350 ml) and Na (20 mg) in MeOH (20 ml) was then added. After cooling, the yellow needles (XI) separated and were collected by filtration.

Recrystallization from DMF gave yellow needles (XI), mp 244—245°. Identity was confirmed by comparing IR spectra and mixed melting point.

14) All melting points were not corrected. The NMR spectra were taken on a Varian A-60-A spectrometer with tetramethylsilane as an internal standard.