mμ (log ε): 220 (4.19). IR ν_{max} cm^{-1}: 3500 (OH), 1780, 1720, 1620 (butenolide). *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.56; H, 8.92.

Reduction of 3β-Acetoxy-14-hydroxy-15-oxo-14β-card-20(22)-enolide (XI) with $NaBH_4$——To a solution of XI[3,5] (52 mg) in MeOH (3 ml) was added $NaBH_4$ (53 mg) at 0° while stirring. The reaction mixture was allowed to stand for 1.5 hr at the same temperature. Working up in the same way as described above yielded a crystalline product (46 mg) whose TLC revealed the presence of IIb and VIIIb, the former predominating. It was recrystallized from MeOH–ether to give IIb (27 mg), mp 243—248°, identical with the authentic specimen[3] in TLC, mixed melting point and comparison of the IR spectrum.

Conversion of VIb into Vb by Treatment with Alumina——To a solution of VIb (2 mg) in a mixture of MeOH (0.5 ml) and $CHCl_3$ (0.5 ml) was added neutral alumina (100 mg, activity grade III—IV[11]), and the mixture was allowed to stand at room temperature for 66 hr. After filtration of the alumina, it was washed with acetone. The combined filtrates were concentrated to dryness giving a crystalline residue (1.5 mg) which was recrystallized from acetone–pet. ether to afford Vb (*ca.* 1 mg), mp 177—178°, identical with an authentic sample in TLC, mixed melting point and comparison of the IR spectrum.

Acknowledgement This work was supported in part by a Grant-in-Aid from the Ministry of Education, which is gratefully acknowledged.

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UDC 547.852.9.04 : 546.18.04

Studies on Heterocyclic Compounds. XV.[1] Synthesis of Furo[2,3-*d*]pyridazine Derivatives. (4).[2] Synthesis of 2-[2-(5-Nitro-2-furyl)vinyl]-4,7-dichlorofuro-[2,3-*d*]pyridazine and Related Compounds by the Wittig Reaction[3]

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For several years 5-nitro-2-furyl derivatives have been of marked biological interest, since it was shown that particularly 5-nitro-2-furylvinyl heterocyclic compounds[5] are highly antibacterial.

The biological activity of some of these compounds encouraged us to prepare 2-[2-(5-nitro-2-furyl)vinyl]-4,7-dichlorofuro[2,3-*d*]pyridazine (IV) by the Wittig reaction.

For the synthesis of IV, 2-methyl-4,7-dichlorofuro[2,3-*d*]pyridazine(Ia)[6] served as the starting material. Reaction of Ia with N-bromosuccinimide (NBS) in anhydrous benzene solution in the presence of α,α′-azobisisobutyronitrile (AIBN)[7] as the catalyst gave 2-bromomethyl-4,7-dichlorofuro[2,3-*d*]pyridazine (IIa) in yield 45%, mp 158—160°.

Similarly, reaction of 2-methyl-7-chloro-4-methoxyfuro[2,3-*d*]pyridazine (Ib) with NBS gave 2-bromomethyl-7-chloro-4-methoxyfuro[2,3-*d*]pyridazine (IIb) and reaction of 2-methyl-

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2) Part XII: S. Yoshina and I. Maeba, *Chem. Pharm. Bull.* (Tokyo), **18**, 842 (1970).
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4) Location: *Tenpaku-cho, Showa-ku, Nagoya.*
5) H. Saikachi and H. Ogawa, *J. Am. Chem. Soc.*, **80**, 3642 (1958); K. Miura and I. Okada, *Chem. Pharm.* Bull. (Tokyo), **13**, 525 (1965); A. Fujita, T. Yamamoto, S. Minami, and H. Takamatsu, *Chem. Pharm. Bull.* (Tokyo), **13**, 1183 (1965); A. Sugihara, *Yakugaku Zasshi*, **86**, 349 (1966).
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4-chloro-7-methoxyfuro[2,3-*d*]pyridazine (Ic) with NBS gave 2-bromomethyl-4-chloro-7-methoxyfuro[2,3-*d*]pyridazine (IIc) in good yield.

In contrast, a similar reaction with 2-methyl-7-chlorofuro[2,3-*d*]pyridazin-4-ol (Id) gave only a 3% yield of 2-bromomethyl-7-chlorofuro[2,3-*d*]pyridazin-4-ol (IId) together with a recovery of Id, but hydrolysis of IIa in methanol gave IId in good yield.

The structure of IIa, IIb, IIc and IId was established from an examination of the nuclear magnetic resonance spectra (see Experimental).

Condensation of halide (IIa) with triphenylphosphine took place smoothly in refluxing benzene, giving the corresponding phosphonium salt (III). Compound (III) readly condensed with 5-nitro-2-furaldehyde to give a mixture of *cis-trans* isomers of 2-[2-(5-nitro-2-furyl)vinyl]-4,7-dichlorofuro[2,3-*d*]pyridazine (IV).

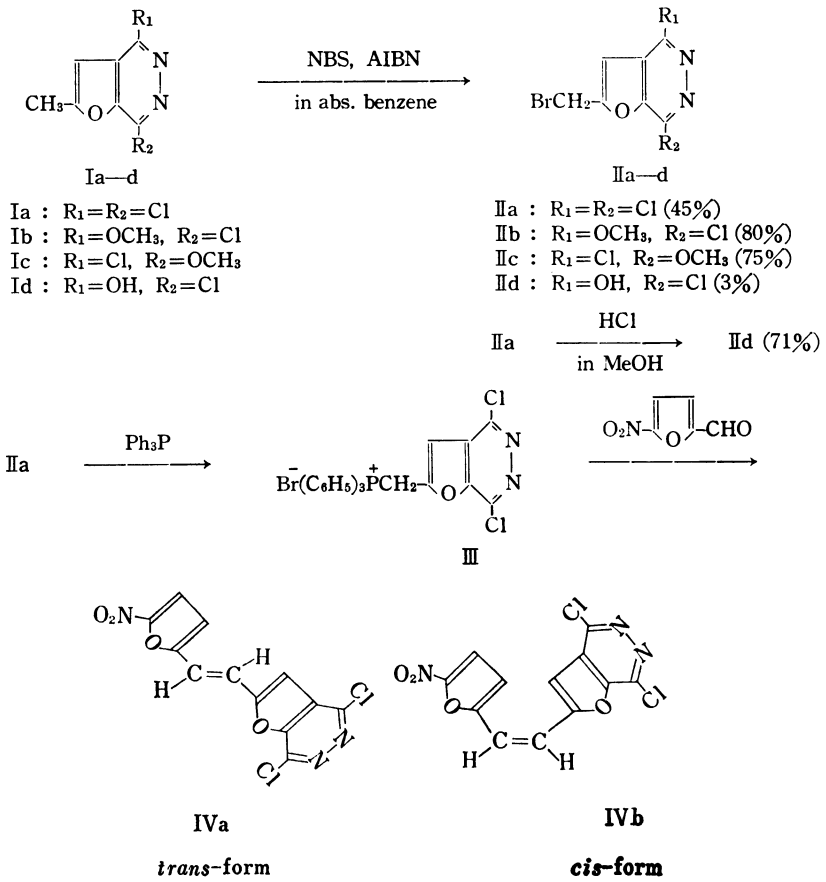


Chart 1

Two isomers of IV were separated by fractional crystallization in 63%, mp 260° (IVa) and 8%, mp 226° (IVb). The mass spectra of both products exhibit a molecular ion peak at *m/e* 325.

The ultraviolet absorption spectrum of IVa in ethanol showed an absorption at 400 mμ (ε 30000) and 382 mμ (ε 37500) and that of IVb at 400 mμ (ε 27200) and 382 mμ (ε 34300). The infrared (IR) absorption spectrum of IVa was different from that of IVb in its fingerprint region as shown in Fig. 1.

Successively, the configurations of IVa and IVb will be discussed in the comparative studies of their nuclear magnetic resonance spectra. In the nuclear magnetic resonance spectra in DMSO-d_6, the structure of IVa was assigned as follows: two protons on the nitrofuran ring (τ 2.23 and 2.86 each doublet J=3.8 cps), two protons on the disubstituted ethylene (τ 2.50 singlet) and one proton on the furopyridazine ring (τ 2.45 singlet), while that of IVb was assigned as follows: two protons on the nitrofuran ring (τ 2.16 and 2.61 each doublet J=3.8 cps), two protons on the disubstituted ethylene (τ 2.99 singlet) and one proton on the furopyridazine ring (τ 2.02 singlet).

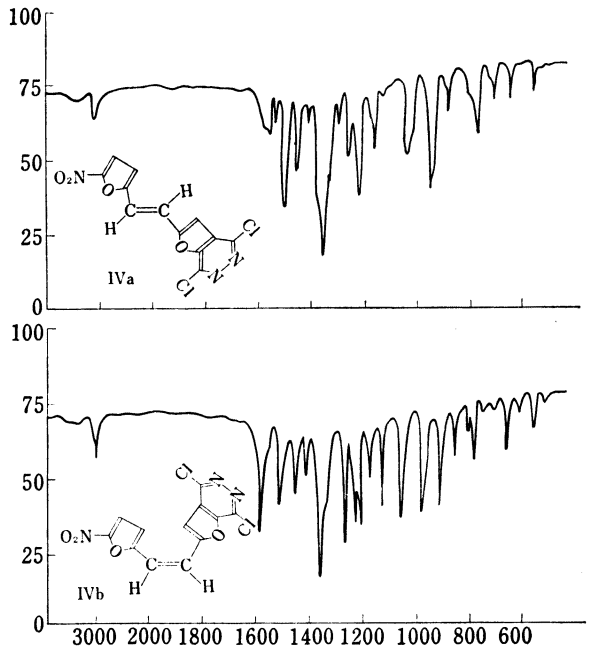


Fig. 1. Infrared Absroption Spectra (in KBr) of IVa and IVb

Curtin, *et al.*[8] have observed that the vinylproton occurs at a higher field for *cis*- than *trans*-stilbene in nuclear magnetic resonance spectra. From the fact that the signal of the vinylprotons of IVb appeared at higher field (τ 2.99) than that of IVa (τ 2.50), the compounds IVa and IVb can be assigned IVa to *trans*- and IVb to *cis*-structure.

Similarly, III condensed with 2-pyridylaldehyde to give a mixture of *cis-trans* isomers of 2-[2-(2-pyridyl)-vinyl]-4,7-dichlorofuro[2,3-*d*]pyridazine (V). Two isomers of V were separated by fractional crystallization in 44%, mp 215—217° (Va) and 26%, mp 144—145° (Vb).

The mass spectra of both products exhibit a molecular ion peak at *m/e* 291. The ultraviolet absorption spectrum of Va in ethanol showed an absorption at 335 mμ (ε 42500) and that of Vb at 335 mμ (ε 18300). In the nuclear magnetic resonance spectra in CF_3COOH, the signal of the vinylproton of Vb at τ 2.63 appeared at higher field than that of Va at τ 1.99.

From these data the compound (Va and Vb) can be assigned Va to *trans*- and Vb to *cis*-structure. Compound (III) condensed with 2-furylaldehyde, 2-thiophene aldehyde and benzaldehyde; single isomers of VI, VII and VIII were crystallized in 67.1, 61.7 and 73% yields, respectively, but no attempt was made to isolate a second isomer in these cases.

Because of the melting point of IX, it could be a mixture of *cis-trans* isomers, but these isomers could not be isolated by fractional crystallization. Therefore, the geometrical configurations of these compounds (VI—IX) were not assigned.

The products which were obtained by the Wittig reaction are described in Table I.

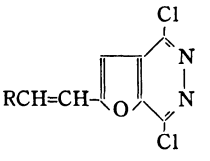
Experimental[9]

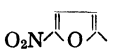
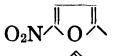
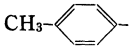
2-Bromomethyl-4,7-disubstitutedfuro[2,3-*d*]pyridazine(IIa—d)——General Procedure: In a flask fitted with a stirrer and a condenser were placed 200 ml of anhydrous benzene, 0.10 mole of Ia—d, 0.10 mole of

8) D.Y. Curtin, H. Gruen and B.A. Shoulders, *Chem. Ind.* (London), **1958**, 1205.

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

TABLE I



Compound	R	mp (°C)	Yield (%)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IVa		260 (*trans*-form)	63	yellow needles	$C_{12}H_5O_4N_3Cl_2$	44.20	1.55	12.89	43.93	1.84	13.16
IVb		226 (*cis*-form)	8	yellow prisms	$C_{12}H_5O_4N_3Cl_2$	44.20	1.55	12.89	44.37	1.63	13.05
Va		216—217 (*trans*-form)	44	colorless needles	$C_{13}H_7ON_3Cl_2$	53.45	2.42	14.38	53.79	2.28	14.22
Vb		144—145 (*cis*-form)	26	colorless prisms	$C_{13}H_7ON_3Cl_2$	53.45	2.42	14.38	53.40	2.37	13.81
VI		200—201	67.1	yellow needles	$C_{12}H_6O_2N_2Cl_2$	51.28	2.15	9.97	50.86	2.25	10.14
VII		>300	61.7	yellow needles	$C_{12}H_7ON_2Cl_2$	48.50	2.04	9.43	48.92	2.37	9.57
VIII		246—248	73	colorless needles	$C_{14}H_8ON_2Cl_2$	57.78	2.77	9.62	57.74	2.82	9.65
IX		230—230	49.5	pale yellow prisms	$C_{15}H_{10}ON_2Cl_2$	59.03	3.30	9.18	58.51	3.25	9.38

N-bromosuccinimide and 1.0 g of α,α'-azobisisobutyronitrile. The mixture was stirred and heated to reflux temperature for 3 hours. The succinimide was filtered from the cooled reaction mixture and the solvent was removed from the filtrate under reduced pressure. The solid residue was recrystallized from iso-propylalcohol.

IIa: Colorless needles, mp 158—160°. *Anal.* Calcd. for $C_7H_3ON_2BrCl_2$: C, 29.82; H, 1.07; N, 9.94. Found: C, 29.64; H, 1.21; N, 10.36. NMR ($CDCl_3$) τ: 2.98 (1H, triplet, $J=1.0$ cps, ring proton 3 pos.), 5.34 (2H, doublet, $J=1.0$ cps, $-CH_2Br$).

IIb: Colorless prisms, mp 160° (decomp.). *Anal.* Calcd. for $C_8H_6O_2N_2BrCl$: C, 34.63; H, 2.18; N, 10.10. Found: C, 34.52; H, 2.45; N, 9.83. NMR ($CDCl_3$) τ: 3.12 (1H, triplet, $J=1.0$ cps, ring proton 3 pos.), 5.40 (2H, doublet, $J=1.0$ cps, $-CH_2Br$), 5.78 (3H, singlet, $-OCH_3$).

IIc: Colorless needles, mp 148° (decomp.). *Anal.* Calcd. for $C_8H_6O_2N_2BrCl$: C, 34.63; H, 2.18; N, 10.10. Found: C, 34.76; H, 2.36; N, 10.39. NMR($CDCl_3$) τ: 3.12(1H, triplet, $J=1.0$ cps, ring proton 3 pos.), 5.40 (2H, doublet, $J=1.0$ cps), 5.70 (3H, singlet, $-OCH_3$).

IId: Colorless needles, mp 193—194°. *Anal.* Calcd. for $C_7H_4O_2N_2BrCl$: C, 31.91; H, 1.56; N, 10.63. Found: C, 32.17; H, 1.90; N, 10.42. NMR (DMSO-d_6) τ: 2.73 (1H, signlet, ring proton 3 pos.), 4.93(2H, singlet, $-CH_2Br$), -3.14(1H, -OH).

Hydrolysis of IIa into IId——Compound (IIa) (6 g) was added to a solution of conc. HCl (0.5 ml) and MeOH (200 ml) and heated in a water bath for 3 hours. The solvent was removed and the residue was recrystallized from iso-propylalcohol to give colorless needles(3.9 g), mp 193—194°.

Phosphonium Salt (III)——0.01 mole (IIa), 0.01 mole (triphenylphosphine) and 30 ml of anhydrous benzene were refluxed for 2 hours. After cooling, the white crystalling precipitate was isolated, washed with 10 ml of benzene and dried, mp 263°. *Anal.* Calcd. for $C_{25}H_{18}ON_2PBrCl_2$: C, 55.18; H, 3.33; N, 5.15. Found: C, 55.37; H, 3.58; N, 4.79.

***trans*-2-[2-(5-Nitro-2-furyl)vinyl]-4,7-dichlolofuro[2,3-*d*]pyridazine (IVa) and *cis*-2-[2-(6-Nitro-2-furyl-2-furyl)vinyl]-4,7-dichlorofuro[2,3-*d*]pyridazine (IVb)**——To a solution of 0.01 mole III and 0.01 mole (5-nitro-2-furaldehyde) in MeOH was added dropwise 10% Na_2CO_3 at room temperature.

The precipitate was filtered off, washed with water. The isomeric mixture was dissolved in acetone and set aside at room temperature for one day. Greenish prisms which separated were filtered off and recrystallized from AcOEt to yield IVb 0.26 g, mp 226°. The filtrate was concentrated and the residue was recrystallized from AcOEt to yield IVa 2.0 g, mp 260°.

***trans*-2-[2-(2-Pyridyl)vinyl]-4,7-dichlolofuro[2,3-*d*]pyridazine(Va) and *cis*-2-[2-Pyridyl)vinyl]-4,7-dichlorofuro[2,3-*d*]pyridazine(Vb)**——Compound(Va and Vb) were made as described above with IVa and IVb.

General Procedure for the Synthesis of 2-Aryl(or Heteryl)vinyl-4,7-dichlorofuro[2,3-*d*]pyridazine(VI—IX)——To a solution of 0.01 mole (III) and 0.01 mole (aromatic or heterocyclic aldehydes) in MeOH was added drop wise 10% Na_2CO_3 at room temperature. The precipitate was filtered off, purified by crystallization from AcOEt. These products are described in Table I.

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UDC 547.92.02.03 : 581.192 : 582.938

Studies on the Constituents of Asclepiadaceae Plants.XXIX.[1] Mass Spectra of C/D *cis* Pregnane Derivatives

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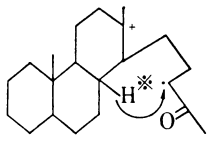
(Received December 8, 1970)

The mass spectra of various derivatives of C/D *cis* polyhydroxypregnane were examined and correlation between mass spectra and the structure was deduced. It was demonstrated that the location of a hydroxy group strongly influences the fragmentation of the skeleton of pregnane derivatives. On the basis of these experimental results, an attempt was made to interpret the mass spectra of related steroids. Tschesche[3] reported that the mass spectra of deacylkondurangogenin A (14β-hydroxy-20-keto-steroid)(X) was strongly affected by the configuration of a side chain at C-17 and giving characteristic differences in the mass spectra of such stereoisomers. The fragmentations reported are 17α-H compound: M^+-28, M^+-46, M^+-74, M^+-85, M^+-89, 17β-H compound: M^+-51, M^+-69, M^+-88, M^+-18, M^+-n·H_2O-$COCH_3$.

We examined the mass spectrum of a 17β-H compound, 3β-acetoxy-14β-hydroxy-5α, 17-isopregnan-20-one, but the spectrum indicated negligible fragment peaks of M^+-51, M^+-69, and M^+-88, while there were abundant fragment peaks of M^+-H_2O, M^+-H_2O-$COCH_3$, and M^+-H_2O-CH_3. Similarly the formation of ions *m/e* M^+-51, M^+-69, and M^+-88 could not be recognised in the mass spectrum of 3β, 11β, 12β-triacetoxy-14β-hydroxy-5α, 17-isopregnan-20-one (17β-H compound), but the peaks which should occur in the 17α-H compound, *m/e* M^+-28, M^+-44, M^+-74, and M^+-89, were detected.



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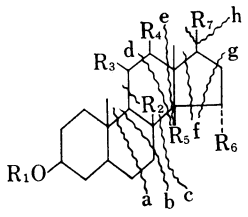

II

Djerassi, *et al.*[4] reported that no difference was observed between the fragmentations of 17 epimers of 5α-pregnan-20-one isotopically labelled at C-8. A reasonable explanation is that the ionizations of both epimers occur through a common intermediate (I).

1) XXVIII: H. Mitsuhashi, K. Hayashi, and K. Tomimoto, *Chem. Pharm. Bull.* (Tokyo), **18**, 828 (1970).
2) Location: *a*) Present address: *National Institute of Hygenic Sciences, Kamiyoga 1-18-1, Tokyo, 158, Japan*; *b*) *Kita-12-jo, Nishi-6-chome, Sapporo, Hokkaido, 060, Japan.*
3) T. Tschesche, P. Welzel, and H.W. Fehlhaber, *Tetrahedron*, **21**, 1797 (1965).
4) L. Tökes, R.T. La Londe, and C. Djerassi, *J. Org. Chem.*, **32**, 1020 (1967).