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Studies on the Syntheses of N-Heterocyclic Compounds. XXVI.[1] Syntheses of Pyrido[3,4-*d*]pyridazine Derivatives. (3)

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A new synthetic route to 1,4-dimorpholino-7-phenylpyrido[3,4-*d*]pyridazine (**1**), a potent diuretic, has been investigated. Chlorination and the subsequent dechlorination by catalytic hydrogenation of ethyl 3-cyano-2-oxo-6-phenyl-4(1H)-pyridinecarboxylate (**2**) gave ethyl 3-cyano-6-phenyl-4-pyridinecarboxylate (**6**), which was also obtained by desulfurization of ethyl 3-cyano-6-phenyl-2-thioxo-4(1H)-pyridinecarboxylate (**3**). **6** was led to 7-phenylpyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (**12**), a key intermediate in the synthesis of **1**, by way of cyclic imide (**10**) or anhydride (**11**). Several homologs of **1** could also be prepared by employing these procedures. Reactivity of the three chloro groups in 1,4,5-trichloro-7-phenylpyrido[3,4-*d*]pyridazine (**18**) towards nucleophilic substitution with morpholine is discussed.

In the preceding papers,[1,3] we reported the syntheses of a potent diuretic, 1,4-dimorpholino-7-phenylpyrido[3,4-*d*]pyridazine (**1**: DS-511). Recent pharmacological investigations of the compound, however, have required **1** labeled with ^{14}C at a specified position in the pyrido[3,4-*d*]pyridazine ring. In order to meet this requirement and find an improved synthetic method of **1**, further exploration of an alternative synthesis of **1** was undertaken.

Ethyl 3-cyano-2-oxo-6-phenyl-4(1H)-pyridinecarboxylate (**2**), prepared by the reaction of cyanoacetamide with ethyl benzoylpyruvate employing a modified procedure of Libermann's method,[4] was chosen as the starting material. Attempted chlorinations of **2** with phosphorus oxychloride or phosphorus pentachloride under a variety of conditions revealed that heating of **2** with phosphorus pentachloride in an inert high-boiling solvent such as chlorobenzene and xylene afforded the desired ethyl 2-chloro-3-cyano-6-phenyl-4-pyridinecarboxylate (**4**) in 47% and 73% yield respectively. In the former case a dichlorinated minor product was yielded, which proved to be 2-chloro-4-(1-chloroethoxycarbonyl)-3-cyano-6-phenylpyridine (**7**) from nuclear magnetic resonance (NMR), elemental analysis and the formation of **4** on treatment with ethanolic hydrogen chloride. The yield of chlorination was further improved by using phenylphosphonic dichloride[5] as the chlorinating agent affording **4** in 96% yield, but the reaction required an elevated temperature as high as 190°. Dechlorination of **4** by catalytic reduction over palladium-charcoal gave ethyl 3-cyano-6-phenyl-4-pyridinecarboxylate (**6**) in a good yield.

The synthesis of **6** was also attained by employing ethyl 3-cyano-6-phenyl-2-thioxo-4(1H)-pyridinecarboxylate (**3**) which was prepared by the reaction of ethyl benzoylpyruvate with cyanothioacetamide[6] in 96% yield. Bubbling of chlorine gas into an acetic acid solution

1) Part XXV: Y. Oka, K. Omura, A. Miyake, K. Itoh, M. Tomimoto, N. Tada, and S. Yurugi, *Chem. Pharm. Bull.* (Tokyo), **23**, 2239 (1975).
2) Location: *Juso, Yodogawa-ku, Osaka, 532, Japan.*
3) S. Yurugi, T. Fushimi, H. Sugihara, and M. Hieda, *Yakugaku Zasshi*, **92**, 1333 (1972).
4) D. Libermann, N. Rist, F. Grumbach, S. Cals, M. Moyeux, and A. Rouaix, *Bull. Soc. Chim. France*, **1958**, 687.
5) G.L. Walford, H. Jones, and T.Y. Schen, *J. Med. Chem.*, **14**, 339 (1971).
6) U. Schmidt and H. Kubitzek, *Chem. Ber.*, **93**, 1559 (1960).

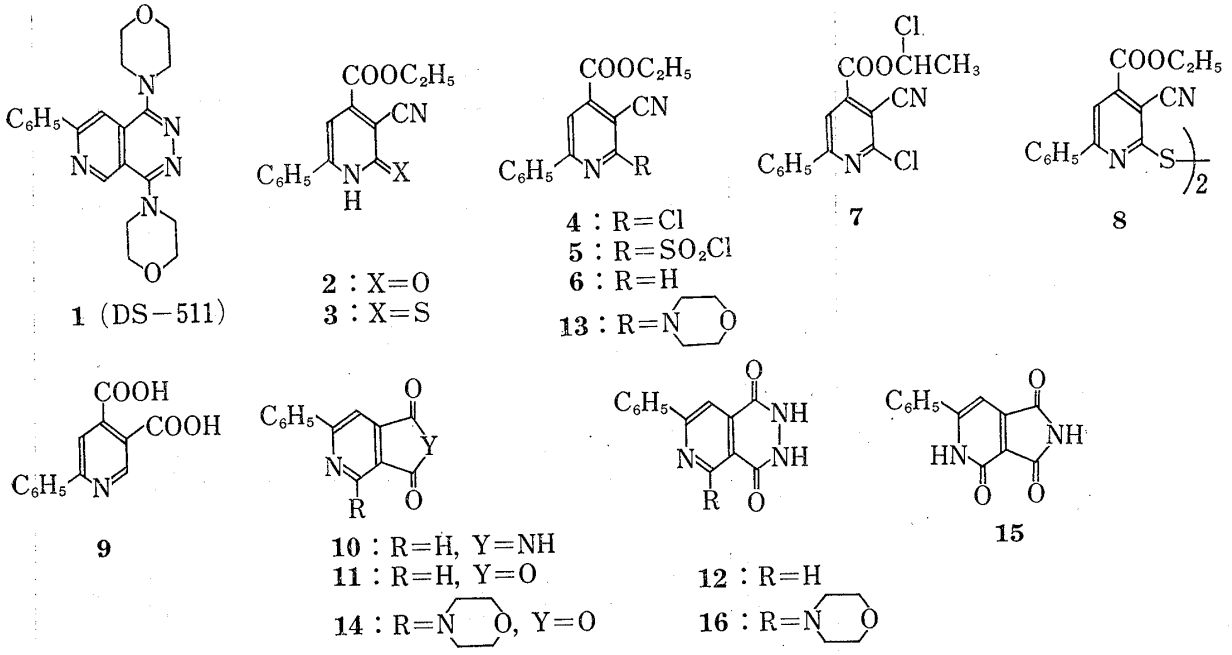


Chart 1

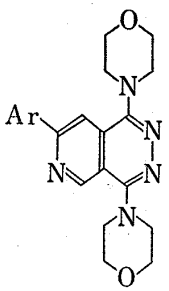
of **3** at 100° gave **4** in 90% yield, whereas the same procedure below 10° afforded ethyl 2-chlorosulfonyl-3-cyano-6-phenyl-4-pyridinecarboxylate (**5**) which was presumed to be an intermediate to **4** from the fact that **5** was readily converted to **4** on heating in acetic acid. On the other hand, **3** could directly be converted to **6** by oxidative or reductive desulfurization. Thus, oxidation of **3** with hydrogen peroxide[7] afforded **6** in 50% yield, while the oxidation with nitric acid[8] yielded bis (3-cyano-4-ethoxycarbonyl-6-phenyl-2-pyridyl)disulfide (**8**) which could be led to **6** by the reaction with hydrogen peroxide. Reductive desulfurization of **3** with Raney nickel afforded **6** in 60% yield.

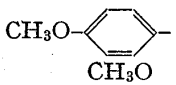
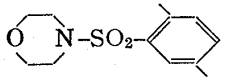
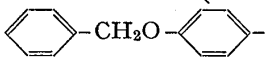
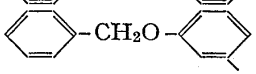
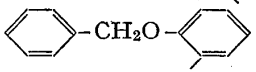
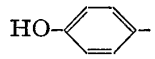
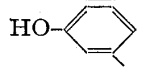
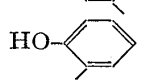
Conversion of **6** into 7-phenylpyrido[3,4-*d*]pyridazine-1,4-(2H,3H)-dione (**12**), a key intermediate in the synthesis of **1**, was achieved *via* two routes: First, treatment of **6** with hot conc. sulfuric acid gave a cyclic imide (**10**), the reaction of which with hydrazine gave **12** in a high yield. Secondly, 6-phenylcinchomeronic acid (**9**) obtained by the alkaline hydrolysis of **7** was led to anhydride (**11**), which was treated with hydrazine to give **12**. The compound **12** obtained by the above methods were identical in every respect with an authentic sample prepared by our earlier methods.[1,3] The synthesis of **1** labeled with ^{14}C at the 4 position of the pyrido[3,4-*d*]pyridazine ring was carried out starting from $N^{14}C\text{-}CH_2\text{-}CONH_2$ *via* the route **2**→**4**→**6**→**10**→**12**→**1**, details of which have been reported in a separated paper.[9]

The above reactions also provided a useful method for the preparation of several homologues of **1** (Table I) which had hitherto been rather difficult to obtain owing to the lability to permanganate oxidation involved in the previous methods.[1,3] Thus, compound **1a**, 2-furyl derivative of **1**, was similarly prepared according to the route **2**→**4**→**6**→**10**→**12**. In the course of the similar process directed to the synthesis of **1b**,[1] it was found that a sulfo group was introduced at the 3 position of 4-methoxyphenyl group during the reaction of **6b** (Table IV) with sulfuric acid, and further reactions of the product *via* the route **6**→**10**→**12**→**1** without purifying each intermediate finally afforded 7-(4-methoxy-3-morpholinosulfonylphenyl)-1,4-dimorpholinopyrido[3,4-*d*]pyridazine (**1c**). Therefore the synthesis of **1b** was carried out according to the route **2**→**4**→**6**→**9**→**11**→**12**. Derivatives **1d**, **1e** and **1f** were prepared starting

7) S. Akabori, *Chem. Ber.*, **66**, 151 (1933).
8) R.G. Jones, *J. Am. Chem. Soc.*, **74**, 1085 (1952).
9) N. Hayashi, K. Shinozaki, and K. Itoh, *J. Takeda Res. Lab.*, **30**, 235 (1974).

TABLE I. 7-Aryl-1,4-dimorpholinopyrido[3,4-*d*]pyridazine



No.	Ar	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
1a		60	214—218	$C_{19}H_{21}O_3N_5$	62.11	5.76	19.06	62.40	5.86	18.67
1b		63	222—223	$C_{22}H_{25}O_3N_5 \cdot 1/2H_2O$	63.43	6.29	16.81	63.22	6.08	16.50
1c		14	172—176	$C_{26}H_{32}O_6N_6S$	54.24	6.13	14.60	54.36	5.53	14.66
1d		58	206—208	$C_{28}H_{29}O_3N_5$	69.54	6.05	14.48	69.54	6.09	13.94
1e		92	181—182	$C_{28}H_{29}O_3N_5$	69.54	6.05	14.48	69.32	5.91	14.00
1f		90	162—164	$C_{28}H_{29}O_3N_5$	69.54	6.05	14.48	69.53	6.07	14.82
1g		72	285—287	$C_{21}H_{23}O_3N_5$	64.11	5.89	17.80	63.98	5.74	17.94
1h		80	277—279	$C_{21}H_{23}O_3N_5 \cdot CF_3COOH$	61.73	5.41	15.65	61.54	5.46	16.11
1i		82	250—253	$C_{21}H_{23}O_3N_5$	64.11	5.89	17.80	64.21	5.99	17.31

with the desulfurization of **3** with Raney nickel to give **6**, followed by the conversions **6**→**9**→**11**→**12**. Treatment of **1d**, **1e** and **1f** with trifluoroacetic acid[10] gave 7-*para*, *meta* and *ortho*-hydroxyphenyl derivatives of DS-511 (**1g**, **1h** and **1i**) respectively.

In the above synthetic route to **1** starting from **2**, two chlorination steps, *i.e.* **2**→**4** and **12**→**1**, are involved. It was assumed that the synthesis would be much simplified if the two steps could successfully be combined. For this purpose the following reactions illustrated in Chart 2 were undertaken. 7-Phenylpyrido[3,4-*d*]pyridazine-1,4,5(2H,3H,6H)-trione (**17**) prepared from **2** *via* cyclic imide (**15**) was chlorinated with phosphorus oxychloride in the presence of N,N-dimethylaniline to give 1,4,5-trichloro-7-phenylpyrido[3,4-*d*]pyridazine (**18**) in 70% yield. Provided if the reaction of **18** with two equivalents of morpholine gave 5-chloro-1,4-dimolpholino derivative (**24**), dechlorination of **24** would lead to a facile synthesis of **1**.

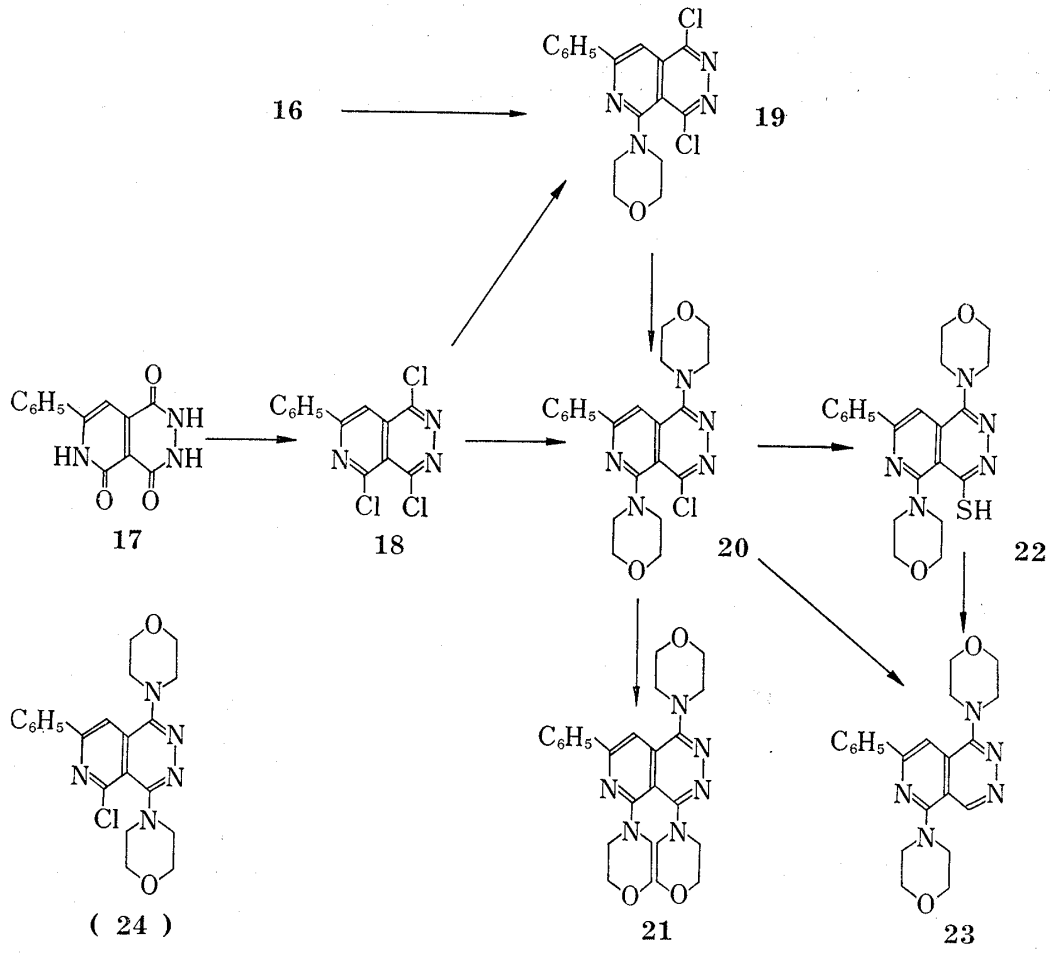


Chart 2

Although reaction of **18** with an excess of morpholine at 130—140° gave 1,4,5-trimorpholino-7-phenylpyrido[3,4-*d*]pyridazine (**21**), a monochloro-dimorpholino derivative (**20**) was obtained when the reaction was carried out in ethanol under reflux. On the other hand, the reaction in chloroform at lower temperature afforded a dichloro-monomorpholino derivative, the structure of which was assigned as 1,4-dichloro-5-morpholino-7-phenylpyrido[3,4-*d*]pyridazine (**19**) by identification with the sample prepared by the following alternative method: Ethyl 3-cyano-2-morpholino-6-phenyl-4-pyridinecarboxylate (**13**) prepared by the reaction of **4** with morpholine was treated with sulfuric acid to give cyclic imide (**14**), which, after being led to 1,4-dione (**16**), was chlorinated to afford **19**. Dechlorination of **20** by catalytic

10) J.P. Marsh Jr. and L. Goodmann, *J. Org. Chem.*, **30**, 2491 (1965).

hydrogenation or desulfurization of mercapto derivative (**22**) prepared by the reaction of **20** with sodium mercaptide gave dimorpholino derivative (**23**). Contrary to our expectation, however, **23** was unidentical with **1**. The fact indicated that one of the two morpholino groups in **23** was substituted at the 5 position. Determination of the substituted position of the other morpholino group, 1 or 4 position, was made by comparison of proton signals in the NMR of the related compounds. As is shown in Chart 3, the proton signal of 8-H in the 1-morpholinopyrido[3,4-*d*]pyridazine derivatives generally appears at higher field compared with the corresponding 1-chloro derivatives. Furthermore comparison of the data for **1**, **26** and **27** shows that the τ-value of 8-H signal is lower in 1-chloro-4-morpholino derivative (**26**) and higher in 4-chloro-1-morpholino derivative (**27**) than that in 1,4-dimorpholino derivatives (**1**). From these observations the value of 2.50 τ for 8-H in **20** appears to indicate that the structure of **20** is 4-chloro-1,5-dimorpholino-7-phenylpyrido[3,4-*d*]pyridazine. **19** was converted to **20**, and **20** in turn to **21** by the reaction with morpholine as the reaction temperature was elevated stepwise. The above results indicate that reactivity of the three chloro groups in **18** towards nucleophilic substitution by morpholine is in the order of 5>1>4 position.

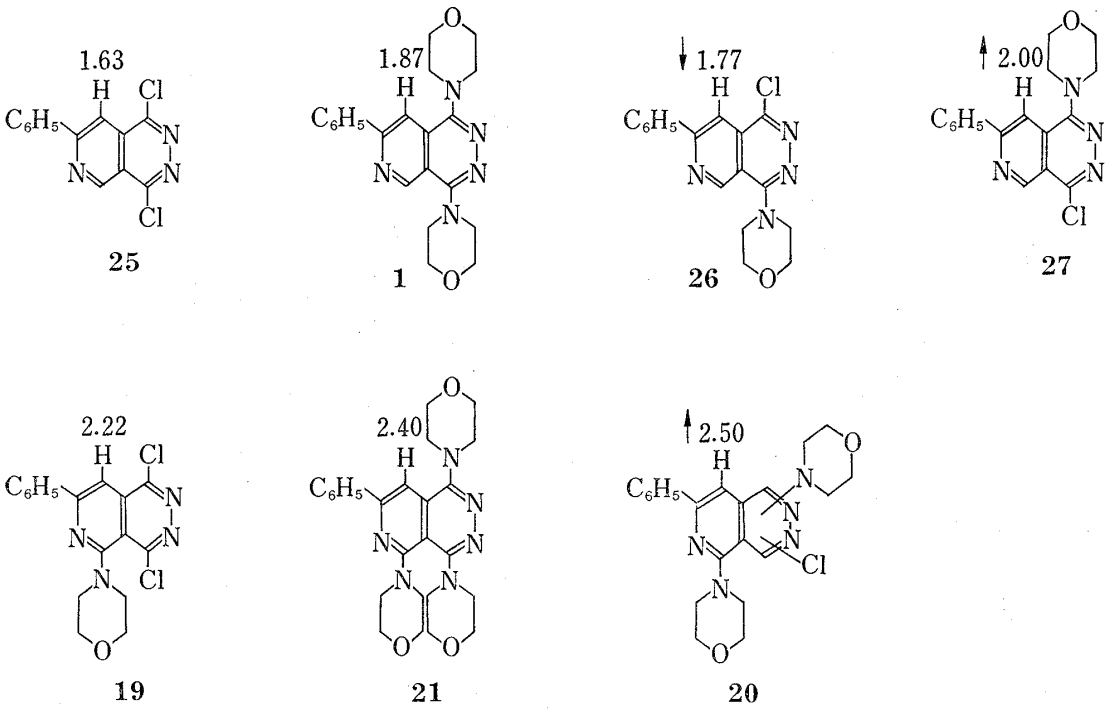


Chart 3. Proton Chemical Shifts in 7-Phenylpyrido[3,4-*d*]pyridazine Derivatives (τ in $CDCl_3$, 60 MHz)

The arrows designate the change of τ-value compared with the corresponding 1,4-dimorpholino derivatives (**1** or **21**).

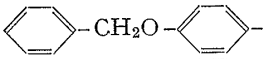
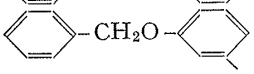
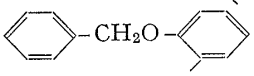
Most of the derivatives listed in Table I exhibited potential diuretic activity. Especially the activities of **1a**, **1b** and **1g** were comparable to that of **1**.

Experimental[11]

Ethyl Acylpyruvate——Ethyl benzoyl-, 2-furoyl- and *p*-methoxybenzoylpyruvate were prepared according to the previously reported method.[1] *o*, *m* And *p*-benzyloxybenzoyl derivatives were also prepared by the similar procedure.

11) All melting points were taken on a Kofler-type hot-stage apparatus (Yanagimoto Co.) and are uncorrected. NMR spectra were measured in $CDCl_3$ on Varian HA-100 or A-60 high resolution spectrometer. Thin-layer chromatography (TLC) was carried out with Silicagel-f Spotfilm (Tokyo Kasei Co.), detected by Dragendorff's reagent or by ultraviolet (UV) fluorescence. Column chromatography was carried out on silica gel (Kieselgel 60, Merck).

Table II. Ethyl Acylpyruvate
$RCOCH_2COCOOC_2H_5$

R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Found C	Found H
	60	124—125	$C_{19}H_{18}O_5$	69.92	5.56	69.95	5.40
	60	58—59	$C_{19}H_{18}O_5$	69.92	5.56	70.04	5.38
	53	71—72	$C_{19}H_{18}O_5$	69.92	5.56	70.04	5.35

Ethyl 6-Aryl-3-cyano-2-oxo-4(1H)-pyridinecarboxylate (2) and the Derivatives——Ethyl acylpyruvate and equimolar cyanoacetamide were dissolved in abs. EtOH with gentle heating. The solution was maintained at 60° in an oil bath, while piperidine or triethylamine was added dropwise with stirring. When the addition of amine was complete, the mixture was stirred for 3 hr under reflux. After cooling the resulting yellow solid was collected by filtration, washed with EtOH and dried to give **2** or the derivatives.

Ethyl 6-Aryl-3-cyano-2-thioxo-4(1H)-pyridinecarboxylate (3) and the Derivatives——The reaction of ethyl acylpyruvate with cyanothioacetamide in the presence of ethanolamine or triethylamine in the same manner as described for the preparation of **2** afforded **3** or the derivatives as red crystalline solid.

Ethyl 6-Aryl-2-chloro-3-cyano-4-pyridinecarboxylate (4)——i) To a solution of ethyl 3-cyano-2-oxo-6-phenyl-4(1H)-pyridinecarboxylate (**2**) (10 g) in xylene (10 ml) was added PCl_5 (23.3 g) and the mixture was warmed in an oil bath to 140° with stirring. When the evolution of hydrogen chloride ceased, the temperature was raised to 150° by additional heating and low boiling fraction was distilled off. After 5 hr the reaction mixture was chilled, poured into a large excess of ice water and extracted with AcOEt. The extract was washed with aq. $NaHCO_3$ and H_2O, dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure to give an oily residue, which was recrystallized from EtOH to afford **4** (7.9 g) as colorless needles.

ii) A mixture of **2** (4 g), PCl_5 (8 g) and chlorobenzene (16 ml) was heated in an oil bath at 140° for 6 hr. The reaction mixture was chilled, poured into a large excess of ice water and extracted with AcOEt. The extract was washed with aq. $NaHCO_3$ and H_2O, dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure to give an oily residue, which was submitted to column chromatography eluted with C_6H_6 to give **4** (2.0 g) and 2-chloro-4-(1-chloroethoxycarbonyl)-3-cyano-6-phenylpyridine (**7**) (0.1 g). Recrystallization of the latter from EtOH gave colorless needles, mp 140—142°. IR ν_{max}^{Nujol} cm^{-1}: 2220 (C≡N), 1760 (C=O). NMR (in $CDCl_3$) τ: 1.72 (1H, s, a pyridine proton), 1.80—2.00, 2.30—2.60 (5H, m, phenyl protons), 3.20 (1H, q, J=6.0 Hz, >CHCl), 8.00 (3H, d, J=6.0 Hz, >CH–CH_3). *Anal.* Calcd. for $C_{15}H_{10}O_2N_2Cl_2$: C, 56.10; H, 3.14; N, 8.72. Found: C, 55.90; H, 2.90; N, 8.71.

iii) A mixture of **2** (5.36 g) and $PhPOCl_2$ (7.8 g) was heated at 180—190° with exclusion of moisture for 4 hr. On cooling the mixture was treated with ice water, and the resulting solid was collected by filtration, washed thoroughly with water and recrystallized from EtOH to give **4** (5.5 g). By the same procedure **4a** and **4b** were prepared.

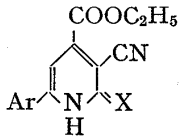
iv) Cl_2 gas was bubbled through a solution of **3** (1 g) in AcOH–H_2O (5: 1, 12 ml), while temperature was kept at 100°. After cooling resulting precipitate was collected by filtration, washed with H_2O and dried. Recrystallization from MeOH gave **4** (0.9 g).

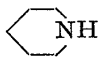
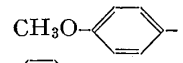
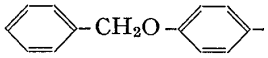
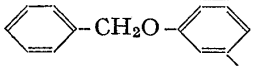
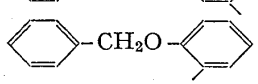
v) Cl_2 gas was bubbled through a solution of **3** (1.3 g) in AcOH–H_2O (5: 1, 12 ml), while temperature was maintained below 10°. The resulting solid was collected by filtration and recrystallized from AcOH to afford ethyl 2-chlorosulfonyl-3-cyano-6-phenyl-4-pyridinecarboxylate (**5**, 1.2 g) as colorless needles. Heating of **5** in AcOH (10 ml) at 140—150° for 1 hr gave **4** (74%).

Ethyl 6-Aryl-3-cyano-4-pyridinecarboxylate (6)——i) A solution of **4** (10 g) and Et_3N (5 g) in EtOH (100 ml) was hydrogenated over 5% palladium-charcoal (1.0 g) at room temperature under atmospheric pressure until 1 equivalent of H_2 was consumed. The mixture was filtered and the filtrate was evaporated under reduced pressure to give an oily residue to which was added H_2O. The resulting solid was collected by filtration, washed thoroughly with H_2O, recrystallized from MeOH to give **6** (6.9 g) as colorless needles. By the same procedure **6a** and **6b** were synthesized.

ii) To a solution of **3** (1.3 g) in AcOH (5 ml) was added dropwise 30% H_2O_2 (2 ml) at 100° with stirring. After 15 min the reaction mixture was poured into H_2O and extracted with AcOEt. The extract was washed with aq. 10% NaOH and H_2O, dried over Na_2SO_4 and evaporated under reduced pressure. Recrystallization of the residue from MeOH gave **6** (0.6 g).

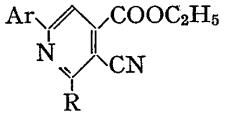
TABLE III. Ethyl 6-Aryl-3-cyano-2-oxo-4(1H)-pyridinecarboxylate and Ethyl 6-Aryl-3-cyano-2-thioxo-4(1H)-pyridinecarboxylate

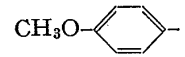
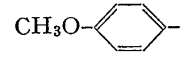
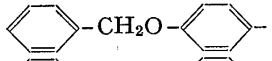
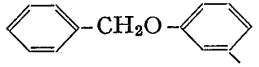
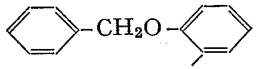


No.	Ar	X	Base	Quantity[a]	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
2		O		0.45	80	273	$C_{15}H_{12}O_3N_2$	—	—	—	—	—	—
2		O	Et_3N	0.14	78	—	—	—	—	—	—	—	—
2a		O	Et_3N	0.3	45	248—251	$C_{13}H_{10}O_4N_2$	60.46	3.90	10.85	60.11	3.79	10.69
2b		O	Et_3N	0.3	62	247—252	$C_{16}H_{14}O_4N_2$	64.42	4.72	9.39	64.32	4.74	9.37
3		S	$HO(CH_2)_2NH_2$	0.015	96	295—297	$C_{15}H_{12}O_2N_2S$	63.38	4.26	9.86	63.09	4.20	9.56
3a		S	Et_3N	0.015	90	155—160	$C_{22}H_{18}O_3N_2S$	67.67	4.65	7.18	67.44	4.53	7.17
3b		S	Et_3N	0.015	90	151—152	$C_{22}H_{18}O_3N_2S$	67.67	4.65	7.18	67.58	4.52	7.21
3c		S	Et_3N	0.015	94	207—209	$C_{22}H_{18}O_3N_2S$	67.67	4.65	7.18	67.62	4.52	6.99

a) milliliter of base per one gram of ethyl acylpyruvate

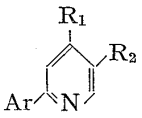
TABLE IV. Ethyl 6-Aryl-3-cyano-4-pyridinecarboxylate Derivatives

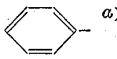
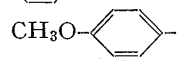
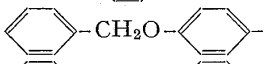
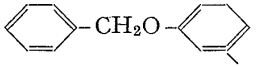
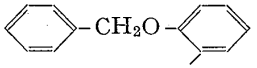
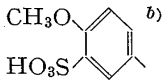
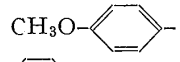
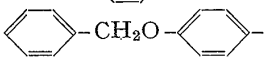
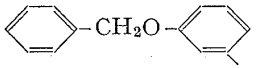
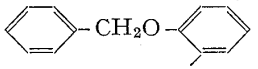


No.	Ar	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4		Cl	74,[a] 47,[b] 96,[c] 90,[d] 74[e]	97—100	$C_{15}H_{11}O_2N_2Cl$	62.83	3.87	9.77	62.74	3.68	9.69
4a		Cl	97[c]	134—136	$C_{13}H_9O_3N_2Cl$	56.43	3.28	10.12	56.12	3.13	10.13
4b		Cl	100[c]	116—118	$C_{16}H_{13}O_3N_2Cl$	60.67	4.14	8.85	60·61	3.95	8.84
5		SO_2Cl	80[d]	145—146	$C_{15}H_{11}O_4N_2SCl$	51.37	3.16	7.99	51.19	3.09	8.00
6		H	79,[f] 50,[g] 75,[h] 47[i]	80—81	$C_{15}H_{12}O_2N_2$	71.41	4.80	11.11	71.39	4.05	11.03
6a		H	35[f]	108—109	$C_{13}H_{10}O_3N_2$	64.46	4.16	11.57	64.30	3.96	11.43
6b		H	78[f]	142—144	$C_{16}H_{14}O_3N_2$	68.07	5.00	9.92	68.01	4.86	10.01
6c		H	30[i]	135—137	$C_{22}H_{18}O_3N_2$	73.73	5.06	7.82	73.81	5.01	7.63
6d		H	36[i]	101—102	$C_{22}H_{18}O_3N_2$	73.73	5.06	7.82	73.11	4.93	7.74
6e		H	28[i]	88—89	$C_{22}H_{18}O_3N_2$	73.73	5.06	7.82	73.69	4.99	7.51

a) chlorination with PCl_5 in xylene,
b) chlorination with PCl_5 in chlorobenzene,
c) chlorination with $PhPOCl_2$,
d) chlorination with Cl_2,
e) thermolysis of **5**,
f) reduction of **4** with H_2/Pd-C,
g) oxidation of **3** with H_2O_2,
h) oxidation of **8** with H_2O_2,
i) desulfurization of **3** with Raney nickel

TABLE V. 6-Arylcinchomeronic Acid Derivatives



No.	Ar	R_1	R_2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
9	 *a)*	COOH	COOH	67	—	$C_{13}H_9O_4N$	—	—	—	—	—	—
9a		COOH	COOH	71	234—235	$C_{14}H_{11}O_5N$	61.54	4.06	5.13	61.19	3.90	5.13
9b		COOH	COOH	98	253—255	$C_{20}H_{14}O_5N$	68.76	4.33	4.01	68.30	4.29	3.84
9c		COOH	COOH	96	223—224	$C_{20}H_{14}O_5N$	68.76	4.33	4.01	68.25	4.39	3.82
9d		COOH	COOH	100	225—226.5	$C_{20}H_{14}O_5N$	68.76	4.33	4.01	68.59	4.44	4.20
10		–CONHCO–		90	256—258	$C_{13}H_8O_2N_2$	69.64	3.60	12.50	69.95	3.66	12.07
10a	 *b)*	–CONHCO–		68	270—274	$C_{11}H_6O_3N_2$	—	—	—	—	—	—
10b	 *b)*	–CONHCO–		75	>300	$C_{14}H_{10}O_6N_2S$	—	—	—	—	—	—
11a		–COOCO–		86	182—184	$C_{14}H_9O_4N$	65.88	3.55	5.49	65.33	3.42	5.27
11b		–COOCO–		83	216—218	$C_{20}H_{12}O_4N$	72.50	3.96	4.23	72.75	3.94	3.99
11c		–COOCO–		75	178—181	$C_{20}H_{12}O_4N$	72.50	3.96	4.23	72.70	3.95	4.00
11d		–COOCO–		84	166—168	$C_{20}H_{12}O_4N$	72.50	3.96	4.23	72.56	3.81	4.16

a) identified with an authentic sample,[1,3]
b) used for the subsequent reaction without purification

iii) A solution of **3** (4.0 g) in a mixture of conc. HNO_3 (d=1.40, 20 ml) and H_2O (50 ml) was refluxed for 6 hr with stirring. On cooling the reaction mixture was poured into H_2O and extracted with $CHCl_3$. The extract was washed with aq. 10% NaOH and H_2O, dried over Na_2SO_4 and evaporated under reduced pressure to give bis(3-cyano-4-ethoxycarbonyl-6-phenyl-2-pyridyl)disulfide (**8**) (3.7 g), mp 181—182°, as colorless needles. *Anal.* Calcd. for $C_{30}H_{22}O_4N_4S_2$: C, 63.60; H, 3.91; N, 9.84. Found: C, 63.30; H, 3.76; N, 9.43. To a solution of **8** (2.7 g) in AcOH (10 ml) heated at 100—110° was added dropwise 30% H_2O_2 (2 ml) with stirring. After 30 min the reaction mixture was poured into H_2O and extracted with AcOEt. The extract was washed with aq. 10% NaOH and H_2O, dried over Na_2SO_4 and evaporated under reduced pressure. The obtained residue was recrystallized from MeOH to give **6** (1.8 g).

iv) To a stirred suspension of Raney nickel (20 g, wet) in EtOH (20 ml) was added **3** (1.0 g), and the mixture was stirred for 1 hr. After removal of Raney nickel by filtration, the filtrate was evaporated under reduced pressure. Recrystallization of the residue from MeOH afforded **6** (0.45 g). Benzyloxyphenylpyridine derivatives (**6c**, **6d** and **6e**) were prepared by the similar procedures.

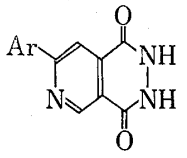
6-Arylcinchomeronimide (10)——General Procedure: A mixture of **6a** or **6b** (5 g) and conc. H_2SO_4 (5 ml) was heated at 100° for 2 hr. On cooling, to the reaction mixture was added H_2O and the resulting precipitate was collected by filtration. Recrystallization from MeOH gave **10**, **10a** or **10b**.

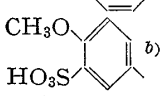
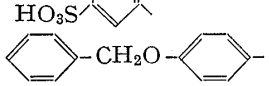
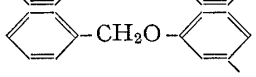
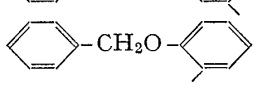
6-Arylcinchomeronic Acid (9)——General Procedure: A mixture of **6** or **6b** (1.0 g) and aq. 10% NaOH (20 ml) was refluxed for 3 hr, and the cooled solution was acidified with conc. HCl. The resulting precipitate was collected by filtration, washed thoroughly with H_2O, and recrystallized from AcOH to give **9** or **9a**. **9b**, **9c** and **9d** were prepared by the similar procedure except that the hydrolysis was carried out in a sealed tube at 150—160° for 3 hr.

6-Arylcinchomeronic Anhydride (11)——General Procedure: A mixture of **9** (4 g) and Ac_2O (50 ml) was refluxed for 1 hr. After chilling the solution, the resulting crystals were collected by filtration and recrystallized from AcOH to give **11**.

7-Arylpyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (12)——i) To a suspension of **10**, **10a** or **10b** (4 g) and AcOH (40 ml) was added hydrazine hydrate (8 ml) and the mixture was refluxed for 1 hr with stirring. After cooling, the resulting precipitate was collected by filtration, washed with H_2O and dried to give **12**, **12a** or **12c** respectively as colorless powder.

TABLE VI. 7-Arylpyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione



No.	Ar	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
12	 [a]	85[c]	—	$C_{13}H_9O_2N_3$	—	—	—	—	—	—
12a	 [b]	69[c]	—	$C_{11}H_7O_3N_3$	—	—	—	—	—	—
12b	CH_3O-	95[d]	>300	$C_{14}H_{11}O_3N_3$	62.45	4.12	15.61	62.05	3.97	15.35
12c	 [b]	43[c]	263—276	$C_{14}H_{11}O_6N_3S$	—	—	—	—	—	—
12d		89[d]	>300	$C_{20}H_{15}O_3N_3$	69.55	4.38	12.17	69.27	4.16	11.83
12e		94[d]	288—291	$C_{20}H_{15}O_3N_3$	69.55	4.38	12.17	68.83	4.37	12.19
12f		83[d]	280—284	$C_{20}H_{15}O_3N_3$	69.55	4.38	12.17	69.59	4.29	12.04

a) identified with an anthentic sample,[1,3]
b) used for the subsequent reaction without purification,
c) obtained from cinchomeronimide (**10**),
d) obtained from cinchomeronic anhydride (**11**)

ii) **11**, **11a**, **11b**, **11c** or **11d** was reacted with hydrazine hydrate in the same manner as in i to give **12**, **12b**, **12d**, **12e** or **12f** respectively as colorless powder.

7-Aryl-1,4-dimorpholinopyrido[3,4-*d*]pyridazine (1) (Table I)——General Procedure: A suspension of **12** or **12a**—**f** (2.0 g), $POCl_3$ (20 ml) and $PhN(CH_3)_2$ (2 ml) was heated at 110° for 3 hr with stirring. The suspension was dissolved slowly during the first hour to give a brown homogeneous solution. After removal of the excess $POCl_3$ by evaporation *in vacuo*, the residue was triturated with cracked ice. The resulting dark purple crystals of crude 7-aryl-1,4-dichloropyrido[3,4-*d*]pyridazine were collected by filtration, dried by suction at room temperature, and immediately submitted to the reaction with morpholine (20 ml) at 130° for 1 hr. The excess morpholine was evaporated under reduced pressure. To the oily residue was added excess H_2O and resulting crude **1** as yellow crystals was collected by filtration and recrystallized from MeOH to give **1** or **1a**—**f** respectively.

7-*p*, *m* or *o*-Hydroxyphenyl-1,4-dimorpholinopyrido[3,4-*d*]pyridazine (1g, 1h or 1i)——A solution of **1d** (7 g) in CF_3COOH (70 ml) was heated under reflux for 0.5 hr. On cooling CF_3COOH was evaporated *in vacuo*. The residue was dissolved in MeOH (20 ml), neutralized with aq. $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, evaporated *in vacuo*, and recrystallized from AcOEt–MeOH to afford pure **1g** (4.7 g). **1h** and **1i** were obtained from **1e** and **1f** respectively by the same procedure.

6-Phenyl-2-oxo-1H-cinchomeronimide (15)——A mixture of **2** (10 g) and conc. H_2SO_4 (35 ml) was heated at 100—110° for 3 hr. To the cooled reaction mixture was added H_2O and the resulting precipitate was collected by filtration to give **15** (8.8 g, 98%). Recrystallization from DMF–ether afforded yellow needles, mp>300°. *Anal.* Calcd. for $C_{13}H_8O_3N_2$: C, 65.00; H, 3.36; N, 11.66. Found: C, 65.03; H, 3.08; N, 11.70.

7-Phenylpyrido[3,4-*d*]pyridazine-1,4,5(2H,3H,6H)-trione (17)——**15** (8.8 g) was added to hydrazine hydrate (88 ml) and the mixture was heated at 140° for 1 hr. On cooling EtOH was added to the mixture and the resulting precipitate was collected by filtration, suspended in H_2O and acidified with aq. 10% HCl to give **17** (6.9 g, 79%) as colorless powder, which was identified with an authentic sample.[3]

1,4,5-Trichloro-7-phenylpyrido[3,4-*d*]pyridazine (18)——**17** (7 g) was reacted with $POCl_3$ (140 ml) and $PhN(CH_3)_2$ (7 ml) as described above in the preparation of **1** to afford **18** (7 g), which was recrystallized from C_6H_6 to give colorless needles.

Ethyl 3-Cyano-2-morpholino-6-phenyl-4-pyridinecarboxylate (13)——A solution of **4** (2 g) and morpholine (16 ml) in EtOH (80 ml) was refluxed for 4 hr and concentrated under reduced pressure. The residue was treated with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated under reduced pressure to give **13** (1.89 g, 77%). Recrystallization from MeOH afforded yellow needles, mp 109—110°. *Anal.* Calcd. for $C_{19}H_{19}O_3N_3$: C, 67.64; H, 5.68; N, 12.46. Found: C, 67.76; H, 5.68; N, 12.46.

2-Morpholino-6-phenylcinchomeronimide (14)——Treatment of **13** (1.7 g) with conc. H_2SO_4 (5 ml) as described above in the preparation of **10** afforded **14** (1.45 g, 93%). Recrystallization from acetone provided a sample suitable for microanalysis, mp 149—152°. *Anal.* Calcd. for $C_{17}H_{15}O_3N_3$: C, 66.01; H, 4.89; N, 13.59. Found: C, 65.68; H, 4.70; N, 13.47.

5-Morpholino-7-phenylpyrido[3,4-*d*]pyridazine-1,4(2H,3H)-dione (16)——A mixture of **14** (1.2 g) and hydrazine hydrate (15 ml) was heated under reflux for 2 hr and excess hydrazine was removed by evaporation under reduced pressure. The residue was acidified with aq. HCl. Filtration of the resulting crystals gave **16** (0.75 g, 59%), mp>300°.

1,4-Dichloro-5-morpholino-7-phenylpyrido[3,4-*d*]pyridazine (19)——i) To ice cooled solution of **18** (3.6 g) in $CHCl_3$ (200 ml) was added dropwise morpholine (5 g) with stirring. After 5 hr $CHCl_3$ was evaporated *in vacuo* at room temperature and the residue was submitted to column chromatography (acetone, C_6H_6= 1: 10) to give **19** (3.1 g) as yellow crystals, which was recrystallized from EtOH. Further elution with the same solvent afforded **20** (0.54 g).

ii) To a suspension of **16** (0.7 g) in $POCl_3$ (11 ml) was added α-picoline (0.5 ml) and the mixture was heated at 110° for 3 hr. After removal of the excess $POCl_3$ by evaporation *in vacuo*, the residue was triturated with cracked ice. The resulting crystals were filtered and recrystallized from EtOH to give **19** (0.3 g).

4-Chloro-1,5-dimorpholino-7-phenylpyrido[3,4-d]pyridazine (20)——i) A solution of **18** (2.0 g) and morpholine (20 ml) in EtOH (200 ml) was refluxed for 2 hr and concentrated under reduced pressure. The resulting precipitate was filtered, and recrystallized from C_6H_6 to afford **20** (1.6 g) as pale yellow needles.

ii) **19** (0.3 g) was reacted with morpholine in the same manner as in i to give **20** (0.25 g), which was identical with the sample prepared by the above method in mixed mp, IR spectrum and TLC (acetone, C_6H_6= 1: 1).

1,5-Dimorpholino-7-phenylpyrido[3,4-*d*]pyridazine-4-thiol (22)——A mixture of **20** (2.0 g) and 10% aq. NaSH (28 ml) in EtOH (200 ml) was heated under reflux for 8 hr and concentrated under reduced pressure. To the residue was added H_2O and acidified with AcOH. The mixture was extracted with AcOEt, washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo* to give **22** (1.9 g). Recrystallization from MeOH afforded yellow needles.

1,5-Dimorpholino-7-phenylpyrido[3,4-*d*]pyridazine (23)——To a solution of **20** (2.0 g) in dioxane (200 ml) was added Et_3N (0.3 g), and the mixture was hydrogenated over 10% palladium-charcoal (2.0 g) at room

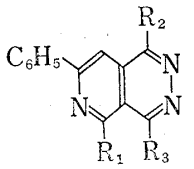
temperature under 50 atm. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (acetone, C_6H_6=1: 4) to give **23** (0.27 g) as colorless needles.

ii) To a suspension of Raney nickel (wet, 20 g) in AcOEt (100 ml) was added **22** (1.0 g) and the mixture was heated under reflux for 2 hr. After filtration, the filtrate was condenced to give an oily residue, which was purified by column chromatography (acetone, C_6H_6=1: 4) to give **23** (0.46 g).

1,4,5-Trimorpholino-7-phenylpyrido[3,4-*d*]pyridazine (21)——i) A mixture of **18** (1.0 g) and morpholine (20 ml) was heated at 130—140° for 6 hr and excess morpholine was removed by evaporation under reduced pressure. To the residue was added H_2O and resulting precipitate was recrystallized from MeOH to give **21** (1.1 g) as yellow needles.

ii) **20** was reacted with morpholine in the same manner as in i to give **21**, which was identical with the sample prepared by the above method in mixed mp, IR spectrum and TLC (acetone, C_6H_6=1: 1).

TABLE VII. 7-Phenyl-1,4,5-trisubstituted Pyrido[3,4-*d*]pyridazine



No.	R_1	R_2	R_3	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
18	Cl	Cl	Cl	82	275—277	$C_{13}H_6N_3Cl_3$	50.27	1.95	13.53	50.33	2.18	13.32
19	N O	Cl	Cl	38,[a] 74[b]	183—185	$C_{17}H_{14}ON_4Cl_2$	56.37	4.17	15.47	56.68	3.97	15.36
20	N O	N O	Cl	60,[b] 73[c]	263—265	$C_{21}H_{22}O_2N_5Cl$	61.23	5.38	17.01	61.50	5.25	16.51
21	N O	N O	N O	74[b]	283—285	$C_{25}H_{30}O_3N_6$	64.91	6.54	18.17	64.53	6.31	17.76
22	N O	N O	SH	95	275—278	$C_{21}H_{23}O_2N_5S$	61.60	5.66	17.11	61.42	5.38	17.13
23	N O	N O	H	30,[d] 50[e]	141—143	$C_{21}H_{23}O_2N_5$	66.82	6.14	18.56	66.55	6.33	18.28

a) chlorination of **16**,
b) obtained from **18**,
c) obtained from **19**,
d) catalytic reduction of **20**,
e) desulfurization of **22** with Raney nickel

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