Pyridazino[3,4,5-*de*]phthalazines. II.[1] Synthesis of nitrogen-substituted derivatives

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Received September 8, 1981

JOHN E. FRANCIS, KARL J. DOEBEL, PAULA M. SCHUTTE, ERNST F. BACHMANN, and ROBERT E. DETLEFSEN. Can. J. Chem. **60**, 1214 (1982).

The synthesis of a wide variety of 9-substituted-3-oxo-3*H*-2,9-dihydropyridazino[3,4,5-*de*]phthalazines (**11**) was achieved by treatment of 3-substituted-3,4-dihydro-4-oxophthalazine-5-carboxylic esters (**10**) with hydrazine hydrate. These esters were prepared from 3-hydroxyphthalide-7-carboxylic acid (**7**) by two different routes. Under basic conditions, alkylation of 3-oxo-3*H*-2,9-dihydropyridazino[3,4,5-*de*]phthalazine (**1**) gave 9-substituted products. These undergo further alkylation at the 2-position. Some of them were converted to 3-chloro, 3-thiono, and 3-hydrazino compounds by standard methods. Dehalogenation of selected 3-chloro compounds or desulphurization of 3-thiono derivatives gave 1-substituted-1*H*-pyridazino[3,4,5-*de*]phthalazines (**22**), some of which were also prepared by direct alkylation of the parent heterocycle **2** under basic conditions. However, treatment of **2** or its 1-methyl homologue with methyl iodide resulted in products in which nitrogen attached to carbon had been attacked rather than the 1- or 9-position. Treatment of the acid chloride of 3,4-dihydro-4-oxophthalazine-5-carboxylic acid with methyl hydrazine led to 2-methyl-3-oxo-3*H*-2,9-dihydropyridazino[3,4,5-*de*]phthalazine (**21***a*) which was purified by cyanoethylation at the 9-position, recrystallization, and hydrazinolysis of the cyanoethyl group. Biological testing revealed that many of the compounds lowered blood pressure in animal models but none had a sufficient therapeutic ratio of activity vs. side effects to warrant clinical trial.

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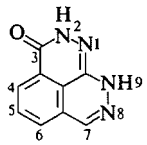
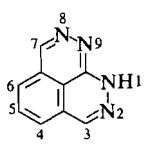
On a réalisé la synthèse d'une grande variété d'oxo-3 dihydro-2,9 3*H*-pyridazino[3,4,5-*de*] phtalazines (**11**) substituées en position 9 en faisant réagir les esters des acides dihydro-3,4 oxo-4 phtalazine carboxyliques-5 (**10**) substitués en position 3, avec l'hydrate d'hydrazine. On a préparé ces esters de deux façons différentes en partant de l'acide hydroxy-3 phtalidicarboxylique-7 (**7**). Dans des conditions basiques, l'alkylation de l'oxo-3 dihydro-2,9 3*H*-pyridazino[3,4,5-*de*] phtalazine (**1**) donne des produits substitués en position 9. Ces derniers subissent une alkylation plus poussée en position-2. On transforme certains de ces composés en composés chloro-3, thiono-3 et hydrazino-3 par des méthodes usuelles. Par déshalogénation de dérivés chlorés en position 3 ou par désulfurisation des dérivés thiono-3, on obtient des dérivés *1H*-pyridazino[3,4,5-*de*] phtalazines (**22**) substitués en position 1. On a préparé certains de ces composés par alkylation directe de l'hétérocycle **2** apparenté en milieu basique. Cependant, la réaction du composé **2** ou de son homologue méthylé en position 1 avec l'iodure de méthyle conduit à des produits dans lesquels l'attaque se fait de préférence au niveau de l'atome d'azote attaché au carbone plutôt qu'au niveau des positions 1 ou 9. La réaction du chlorure de l'acide dihydro-3,4 oxo-4 phtalazine carboxylique-5 avec la méthylhydrazine conduit à la méthyl-2 oxo-3 dihydro-2,9 3*H*-pyridazino[3,4,5-*de*] phtalazine (**21***a*) que l'on a purifiée par cyanoéthylation en position 9, recristallisation et hydrazinolyse du groupe cyanoéthyle. Les tests biologiques ont révélé que plusieurs de ces composés abaissent la pression sanguine chez les animaux choisis à titre de modèles, mais qu'aucun d'eux n'a un rapport thérapeutique suffisant par rapport aux effets secondaires pour justifier des essais cliniques.

[Traduit par le journal]

In the first publication of this series (1) we illustrated the importance of structure **1** as a key intermediate in the synthesis of the desired compounds **2** and **3**.[3]



1



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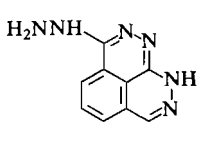

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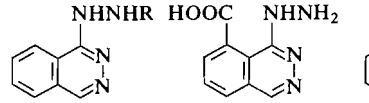
Just as structure **2** represents an internal *hydrazone* of the drug hydralazine (**4***a*), so **1** represents an internal *hydrazide* derived from 4-hydrazinophthalazine-5-carboxylic acid (**5**).



4*a* R = H
4*b* R = $COCH_3$
4*c* R = $COOC_2H_5$

5

6

Although hydrazones of hydralazine were prepared and studied for their hypotensive activity (2), hydrazides received little attention because attempted preparation of some examples led to con-

[1]Part I of this series is ref. 1.

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[3]Placement of hydrogen at the 9-position in structures **1** and **3** represents one tautomeric form of the structure. In the case of **1** the reason for this assignment will become apparent.

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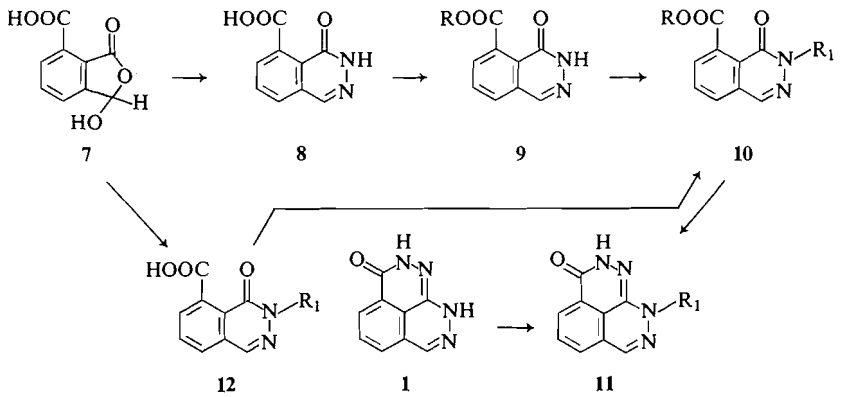


SCHEME 1

densed triazoles which showed no hypotensive activity (2, 3). The first isolated metabolite of hydralazine was not the *N*-acetyl derivative **4***b* as first reported (4) but rather the hydrate of 3-methyl-[1,2,4]-triazolo[3,4-*a*]phthalazine (**6**) (2, 5). The drug todralazine (ecarizine) **4***c*, marketed by Polfa–Pabianice as Binazin®, illustrates that an acylated derivative, albeit a urethane, shows hydralazine-like activity (6). In initial tests, compound **1** showed no activity, but we attributed this possibly to poor absorption. Accordingly, we searched for methods of introducing substituents on one or more of the nitrogens of **1** as a route, not only to a variety of readily absorbed derivatives of **1**, but also to examples of *N*-substituted derivatives of **2** and **3**, thus allowing further exploration of the tricyclic ring system as a possible drug template.

The derivatives of **1** which received our greatest attention were those substituted at the 9-position since they are direct analogs of **1** and potential precursors of *N*-substituted derivatives of **2** and **3**. They were prepared by pathways illustrated in Scheme 1.

As described previously (1), the key intermediate **7** was converted to the phthalazinone acid **8** with aqueous hydrazine in alcohols or acetic acid at reflux. This acid was then esterified to **9**, either the methyl ester **9***a* or the ethyl ester **9***b*, via the acid chloride. Alkylation of the amide nitrogen was accomplished with an alkyl halide in the presence of aqueous sodium hydroxide in an alcohol, or with sodium methoxide in dimethylsulphoxide, or, in two examples, with sodium amide in dimethylsulphoxide. The resulting ester was heated under reflux with aqueous hydrazine to afford the target **11**. Although this route was suitable for alkyl or aralkyl substituted compounds, a more versatile route to **10** involved the reaction of **7** with a monosubstituted hydrazine in alcohol, acetic acid, or water to yield the acid **12** which was then esterified to **10**. This method was used to prepare alkyl-, aryl-, and heterocyclic-substituted products and though often used for the synthesis of 2-aryl-1(2*H*)-phthalazinones (7) it is less commonly illustrated for 2-alkyl-1(2*H*)-phthalazinones (8). Since we have used this method extensively, further explanation for our structure assignments is in order. From 1(2*H*)-phthalazinone, four *N*- or *O*-methylated products can be obtained, all readily differentiated by melting point (9–15). Their structures were only recently confirmed and further characterized by spectroscopy (15–17) and mass spectrometry (18). The only reported method of preparing the *O*-methylated derivative **13** requires conversion of the hydrazide to 1-chlorophthalazine followed by sodium methoxide treatment (9, 10). *O*-Alkylated products are clearly ruled out in our examples since they would react with hydrazine to form structure **1**. In addition, more than two dozen examples of structures **12** (Table 1) and **10** (Table 2) showed strong ir absorption in the range 1640 to 1705 cm^{-1} (Nujol). In the model compounds, it is reported that **14** and **15** show peaks in this region whereas **13** shows two peaks out of this range at 1550 and 1590 cm^{-1} (16). Preparation of the inner salt **15** appears to require a strong alkylating agent under vigorous conditions followed by removal of the proton with base (16) whereas alkylation of the preformed anion or alkylation in the presence of base clearly favours formation of **14** (15, 19–21). The inner salt **15** is converted photochemically in water to the amide **14** but, with acetonitrile as

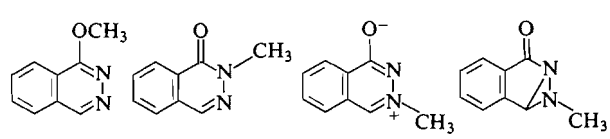
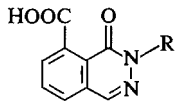
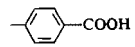
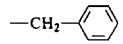
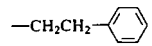
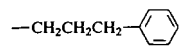
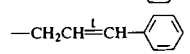
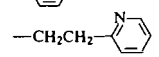
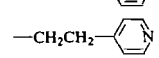


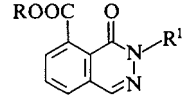
TABLE 1. Phthalazinone acids

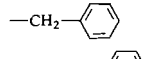
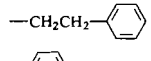
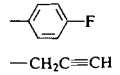
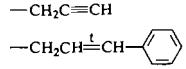
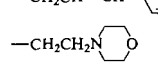
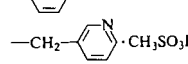
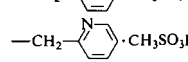


No.	R	Method	Melting point (°C)	Yield (%)	Recrystallization solvent	Infrared (cm^{-1}) ν(C=O)	^{1}Hmr (δ) (DMSO-d_6) H at C-1
12*a*	$-CH_3$	A	228–231	80[a]	H_2O	1695, 1800–2200[c]	8.55
12*b*		A	197–198	87[a]	Benzene	1665, 1705[c]	8.7
12*c*		B	234–237	85[a]	EtOAc	1655, 1695[c]	8.7
12*d*		A	333–339 dec.	77[a]	$MeOCH_2CH_2OH$, DMF–H_2O	1660, 1690, 1715[c]	8.75
12*e*		B	249–253	85[a]	EtOAc, EtOH–H_2O	1695, 1710[d]	8.7
12*f*	$-CH_2CH_2OH$	A	165–168	59[a]	H_2O	1640, 1695[c]	8.55
12*g*		B	168–171	70[a]	EtOH, benzene–hexane	1650, 1710[c]	8.6
12*h*		B	119–122	57[b]	EtOH–H_2O	1650, 1705[c]	8.55
12*i*		C	115–117	62[a]	MeOH, benzene–hexane	1695, 1800–2200[c]	8.55
12*j*		C	164–166	39[b]	Benzene–hexane	1705, 1800–2250[c]	8.6
12*k*		A	273–277	86[a]	EtOH–H_2O	1660, 1695[c]	8.8
12*l*		A	205–207	62[a]	H_2O	1650, 1690[c]	8.55
12*m*		A	226–230	66[a]	H_2O	1640, 1700[c]	8.6

[a]Crude yield.
[b]Pure yield.
[c]Taken in Nujol.
[d]Taken in KBr.

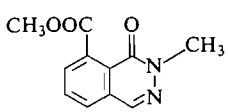
TABLE 2. Phthalazinone esters



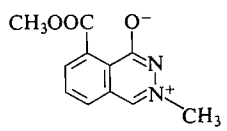
No.	R	R^1	Method[a]	Melting point (°C)	Yield (%)	Recrystallization solvent	Infrared (cm^{-1}) ν(C=O)	^{1}Hmr (δ) (DMSO-d_6) H at C-1
10*a*	CH_3	$-CH_3$	A	125–126	87[b]	H_2O	1730, 1650[e]	8.6
10*b*	CH_2CH_3	$-CH_3$	B	103–104.5	48[c]	C_2H_5OH	1730, 1650[e]	8.6
10*c*	CH_2CH_3		B	150–151	90[b]	C_2H_5OH	1740, 1670[f]	8.75
10*d*	CH_2CH_3		B	147–149	95[c]	C_2H_5OH	1740, 1670[e]	8.6
10*e*	CH_3		B	113–114	87[b]	CH_3OH	1720, 1645[e]	8.65
10*f*	CH_3		B	138–140	91[b]	CH_3OH	1720, 1670[e]	8.7
10*g*	CH_3	$-CH_2C{\equiv}CH$	A	162–164	46[b]	CH_3OH	1720, 1640[g]	8.65
10*h*	CH_3		C	123–124	66[b]	$CHCl_3$–hexane	1730, 1650[e]	8.6
10*i*	CH_3		A	93–96	27[c]	CCl_4–Et_2O	1730, 1650[e]	8.6
10*j*	CH_2CH_3		B	132–134	87[b]	EtOH; EtOAc	1730, 1665[g]	8.75
10*k*	CH_3		C D	178–180	32[d] 65[d]	MeOH–Et_2O	1730, 1660[e]	8.65
10*l*	CH_3		D	171–173	59[d]	EtOH	1735, 1660[e]	8.65

[a]Methods: A, from **11** with alkyl halide/NaOH; B, from **14**; C, from **11** with alkyl halide/sodium methoxide; D, from **11** with alkyl halide/$NaNH_2$.
[b]Before crystallization.
[c]Pure.
[d]As free base.
[e]Taken in Nujol.
[f]Taken in $CHCl_3$.
[g]Taken in KBr.

solvent, the intermediate **16** was isolated, which was readily converted to **14** in acid or water (15). The carbonyl frequency of **16** at 1750 cm^{-1} is out of the range of our phthalazinones. Conversion of **7** to **12***a* (**12**: $R^1 = CH_3$) gave the same product as obtained by saponification of **10***b* (**10**: $R = CH_2CH_3$, $R^1 = CH_3$). The synthesis of **14** from phthalaldehydic acid and methylhydrazine is apparently unreported (22)[4] although 2-(dibromomethyl)-benzoic acid, a phthalaldehydic acid precursor (23), reacts with methylhydrazine in ethanol to give **14** in 75% yield (24). We reacted methylhydrazine with phthalaldehydic acid in refluxing acetic acid and obtained **14** in 81% yield. For further confirmation of the structure, we reacted **9***a* with methyltosylate in refluxing chlorobenzene overnight to obtain the tosylate salt from which the inner salt **17**, an isomer of **10***a* (**10**: $R = R^1 = CH_3$), was obtained by reaction with zinc hydroxide. Our phthalazinone esters (Table 2) display a singlet in the ^{1}Hmr spectrum in the range 8.55–8.75 δ (DMSO-d_6) whereas **17** has a singlet at slightly lower field (8.8 δ) and the tosylate salt a peak well downfield at 10.2 δ. Structure assignment based on the methyl signals is not well defined as it is for **14** and **15**, since all signals in **10***a* and **17** fall in the range 3.65–4.1 δ. More convincing evidence for the structure of **17** is based on infrared analysis. Structure **10***a* showed strong carbonyl absorption at 1730 cm^{-1} (ester) and 1650 cm^{-1} (hydrazide) in Nujol, whereas **17** showed a strong ester band at 1730 cm^{-1} and bands at 1610 and 1555, not attributable to a cyclic hydrazide. Since the structures of **10** and **12** are now established, the structure assignment of **11** must follow. Many examples of **11** were prepared by direct alkylation of **1**, thus supporting the isomer with H at C-9 as the most reasonable depiction of the basic building block **1**.



10*a*



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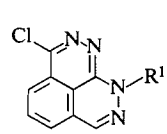
The conversion of **9** to **11** was done in some examples without purification of **10**, generally in low overall yields. Fortunately, the tricyclic structures were well separated from impurities in an aqueous work-up from which the target compounds separated as bright yellow recrystallizable solids. This ease of preparation was also helpful in those examples prepared from **1**. The anion of **1** was preformed with sodium methoxide in dimethylsulphoxide and the alkyl halide added, whereupon the target compounds were obtained in 18 to 88% yields (Table 3). In most examples, no attempts were made to optimize yields although example **11***a* (**11**: $R^1 = CH_3$) was rerun several times by different routes. It was prepared from 3-dibromomethylphthalic anhydride (1) via **8**, **9***a*, and **10***a* in 74% overall yield, via **12***a* and **10***a* in 33% yield, and in two steps via **1** in 18% yield.

As observed with **1**, the 9-substituted compounds **11** could be converted to the corresponding 3-chloro compounds **18** (Table 6), usually with a phosphoryl chloride/phosphorous pentachloride mixture.

Reaction of **11** with phosphorous pentasulphide in pyridine led to structures of type **19**, as exemplified for R^1 = methyl (**19***a*), phenyl (**19***b*), and *N*-morpholinoethyl (**19***c*). Treatment of **18** or **19**



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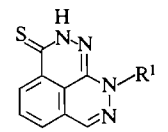
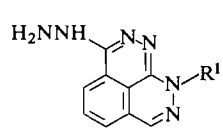


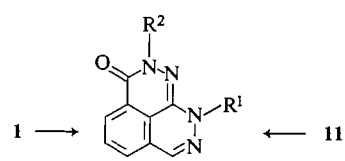
19



20

with hydrazine hydrate produced the hydrazines **20**, illustrated for R^1 = methyl (**20***a*), phenyl (**20***b*), and benzyl (**20***c*). Since most tricyclic compounds were soluble in dimethylsulphoxide, the ^{1}Hmr spectra were almost all run in DMSO-d_6. We noticed in all examples of **19** and in the spectra of **20***c* and the benzylidene hydrazone of **20***b* that the proton at C-4 appeared as a doublet of doublets shifted downfield from the other aromatic protons. This did not appear in any examples of **11** run in DMSO-d_6, nor in **20***a*, run in D_2O. However, **11***j* (**11**: $R^1 = CH_2CH_2CH_2C_6H_5$) was soluble in $CDCl_3$ and this spectrum showed the shifted doublet of doublets centred at 8.35 δ.

Inferior yields of **11** via direct alkylation of **1** were due in part to a second alkylation occurring at the 2-position. One such compound, **21***f* (**21**: $R^1 = R^2 =$ *N*-morpholinoethyl) (Table 4), was isolated as a by-product of the synthesis of **11***g* (**11**: $R^1 =$ *N*-morpholinoethyl). Generation of the anion of **11** with sodium methoxide followed by alkyl halide



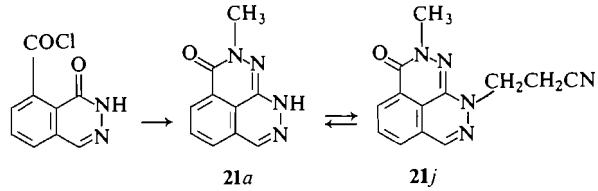
21

[4]Several Russian references were unavailable to us in the original form and their abstracts do not mention the method of synthesis of **14**.

produced other examples of **21**, in which R^1 and R^2 could be the same or different, in yields as high as 95%. When **1** was treated with two moles of sodium methoxide followed by two moles of alkyl halide, the yields of **21** were generally low with **11** as the principle by-product. The structure assignment of **21** is based on a strong carbonyl band in the infrared in the range 1620–1645 cm^{-1} (Nujol). Also, a sharp singlet at 7.85–8.15 δ in the ^{1}Hmr spectrum corresponds to the proton at C-7, comparable to that in examples of **11**, where the range is 7.8–8.1 δ. As observed for **11**, structure **21***b* (**21**: $R^1 = R^2 = CH_3$) shows a doublet of doublets shifted downfield corresponding to the proton at C-4 in $CDCl_3$ but not in DMSO-d_6.

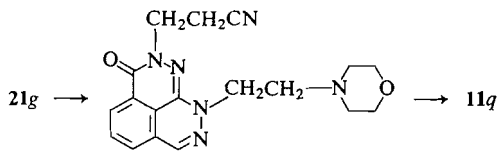
In contrast to the usual alkylation, cyanoethylation of **1** proceeds in high yield. With at least two (preferably three) moles of acrylonitrile in 50% aqueous pyridine with a catalytic amount of Triton B, **21***g* (**21**: $R^1 = R^2$ = cyanoethyl) was obtained in yields exceeding 90%. Attempted monocyanoethylation of **1** produced a mixture of **21***g* and **1** and no detectable amount of the expected product. Since cyanoethylation of **9***a* followed by hydrazine hydrate produced only **1** we were frustrated in our attempt to obtain the monocyanoethyl compound, but instead discovered a method for removing the cyanoethyl group cleanly in our series. This was confirmed by smooth conversion of **21***g* to **1** with hydrazine hydrate. The process was not simply a matter of base catalysis, since excess Triton B in one experiment produced partial hydrolysis of one of the cyanoethyl groups of **21***g* to a carboxyethyl group with no loss of the side chain. Acid stability of the group was also evident, since 80% sulphuric acid converted **21***g* to the diamide **21***i* (**21**: $R^1 = R^2$ = carbamoylethyl) in moderate yield. Under the same cyanoethylation reaction conditions, crotononitrile reacted sluggishly with **1** to give a poor yield of the dialkylated product **21***h* and a considerable recovery of starting material.

The decyanoethylation process was used advantageously in the synthesis of the only derivative of **1** in which only the 2-position was substituted. The acid chloride of **8** was reacted with methylhydrazine in hot chlorobenzene in an effort to prepare **21***a* (**21**: R^1 = H, $R^2 = CH_3$). Since the reaction of methylhydrazine with acid chlorides or anhydrides to produce mainly 1-acyl-1-methylhydrazines is well documented (25), we obtained the desired product, but contaminated with an impurity not readily removed by crystallization. Thus the crude product was cyanoethylated to **21***j*, recrystallized, and decyanoethylated with hydrazine hydrate to yield pure **21***a*.



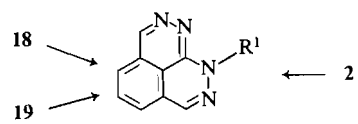
21*a* **21***j*

Removal of the cyanoethyl group was not only achieved with hydrazine hydrate but also in the following example. When **21***g* was treated with morpholinoethyl chloride in the presence of sodium methoxide in dimethylsulphoxide, the cyanoethyl group at the 9-position was replaced by morpholinoethyl in 35% yield. Proof of the assigned structure **21***e* rested on its conversion to **11***q* by treatment with hydrazine hydrate. Since the yield of **21***e* was mediocre and no attempt was made to isolate other products from the mother liquor, we cannot state that replacement occurs exclusively at position 9. No detailed study of the reaction was made, since products such as **21***e* and **11***q* could be prepared by more straightforward methods. However, the illustrated transformations might find application in the preparation of derivatives of other nitrogen heterocycles.



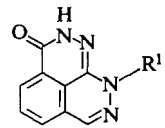
21*g* → **21***e* → **11***q*

Derivatives of **2**, i.e. **22**, were prepared by dehalogenation of chloro compounds **18**, by desulphurization of **19**, and by direct alkylation of the parent heterocycle **2** (Table 5). Dehalogenation was achieved with red phosphorous in 47% hydriodic acid and desulphurization was done with Raney nickel. Direct alkylation took place when the anion was first generated with base. Cyanoethylation of **2**, as described for **1**, gave the desired product **22***e* (**22**: R^1 = cyanoethyl) although in only 24% yield after purification. Treatment of **22***e* with 10% aqueous sodium hydroxide at reflux followed by acidification gave the acid **22***f* (**22**: R^1 = carboxyethyl) in 82% yield. Generally the yields on direct alkylation were poor and required column chromatography before recrystallization. From the few



22

TABLE 3. 9-Substituted-3-oxo-3*H*-2,9-dihydropyridazino[3,4,5-*de*]phthalazines



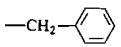
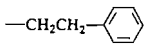
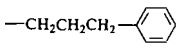
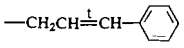
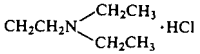
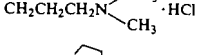
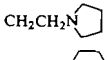
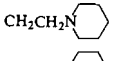
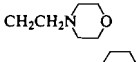
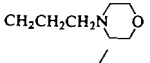
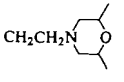
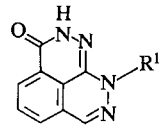
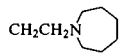
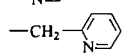
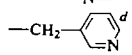
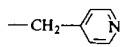
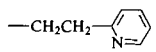
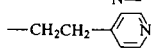
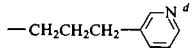
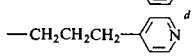
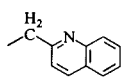
No.	R	Method[a]	Melting point (°C)	Yield (%)	Recrystallization solvent	Infrared (cm^{-1}) ν(C=O), Nujol	^{1}Hmr (δ) (DMSO-d_6) H at C-7
11*a*	$-CH_3$	A	292–296	75[c]	$CH_3OCH_2CH_2OH$	1650	7.8
11*b*	$-CH(CH_3)_2$	C	258–259	30[b]	EtOH	1655	7.95
11*c*	$-CH_2CH_2CH_2CH_3$	D	189–194	56[b]	Benzene	1640	8.0
11*d*	$-CH_2CH_2OH$	A	248–250	86[b]	$CH_3OCH_2CH_2OH$	1640	7.9
11*e*	$-CH_2CH=CH_2$	C	219–222	24[c]	EtOH	1645	7.95
11*f*	$-CH_2CH=CHCH_3$	C	238–240	25[c]	EtOH–$CH_3OCH_2CH_2OH$	1650	8.1
11*g*		A	254–257	89[b]	DMF	1655	8.1
11*h*		D	239–243	66[b]	EtOH	1645	8.05
11*i*		A	203–205	96[b]	$CHCl_3$	1650	7.95
11*j*		A	170–172	95[b]	Benzene–hexane	1650	7.95
11*k*		C	218–220	55[c]	$CH_3OCH_2CH_2OH$	1655	7.95
11*l*	$CH_2CH_2N(CH_3)_2$	C	197–199	19[c]	Benzene	1650	7.95
11*m*		C	280 dec.	35[c]	—	1650	7.8
11*n*		C	290 dec.	5[c]	—	1645	7.7
11*o*		C	192–194	31[c]	EtOH	1650	7.9
11*p*		D	178–180	22[b]	Benzene–cyclohexane	1645	8.0
11*q*		D	203–205.5	25[b]	H_2O	1645	8.0
11*r*		C	180–183	38[c]	EtOH	1645	7.95
11*s*		C	203–205	35[c]	EtOH	1650	8.0

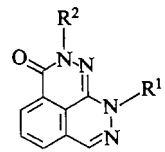
TABLE 3 (*Concluded*)



No.	R	Method[a]	Melting point (°C)	Yield (%)	Recrystallization solvent	Infrared (cm^{-1}) ν(C=O), Nujol	^{1}Hmr (δ) (DMSO-d_6) H at C-7
11*t*		C	183.5–186.5	55[b]	EtOH	1655	7.95
11*u*		B	261–262	8[c]	EtOH	1650	8.2
11*v*		C	275.5–276.5	18[c]	EtOH	1650	8.1
11*w*		C	261–263	16[c]	CH_3OH	1655	8.05
11*x*		C	253–255	10[c]	EtOH	1650	8.0
11*y*		D	235–239	18[b]	EtOH	1655	7.85
11*z*		A	200.5–203	43[c]	EtOH	1645	7.9
11*aa*		C	207–212	13[c]	MeOH–Et_2O	1650	7.95
11*bb*		C	216–218	21[c]	EtOH	1655	8.0
11*cc*		A	233 dec.	50[c]	—	1650	8.2

[a]Methods: A, from **12**; B, from **14**; C, from **11**; D, from **1**.
[b]Before recrystallization.
[c]Purified yield.
[d]Methanesulphonate salt.

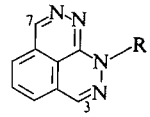
TABLE 4. 2,9-Disubstituted-3-oxo-2,9-dihydropyridazino[3,4,5-*de*]phthalazines

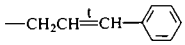
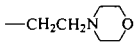
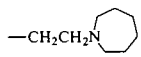
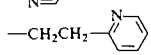


No.	R^1	R^2	Method[a]	Melting point (°C)	Yield (%)	Recrystallization solvent	Infrared (cm^{-1}) ν(C=O)	^{1}Hmr (δ) (DMSO-d_6) H at C-7
21*a*	H	CH_3	E	307–311	77[c]	—	1630, 1655[d]	7.85
21*b*	CH_3	CH_3	A B	195–197	24[c] 93[b]	CH_3OH	1640[d] 1650[e]	7.85
21*c*	CH_3	CH_2CH_2N⟨O⟩	B	176–179	65[c]	Benzene	1645[d]	7.8
21*d*		CH_2CH_2N⟨O⟩	B	162–164.5	40[c]	Isopropanol	1645[d]	8.15
21*e*	CH_2CH_2N⟨O⟩	CH_2CH_2CN	C	195–198	24[c]	CH_3OH	1650[d]	8.05
21*f*	CH_2CH_2N⟨O⟩	CH_2CH_2N⟨O⟩	A	179–182	1.5[c]	EtOAc	1645[d]	7.95
21*g*	CH_2CH_2CN	CH_2CH_2CN	A	188–191.5	92[c]	EtOH	1645[d]	8.05
21*h*	$CH(CH_3)CH_2CN$	$CH(CH_3)CH_2CN$	A	168–170	29[f]	$CHCl_3$–Et_2O	1645[d]	8.0
21*i*	$CH_2CH_2CONH_2$	$CH_2CH_2CONH_2$	D	234–238	58[c]	H_2O	1620, 1650[d]	8.0
21*j*	CH_2CH_2CN	CH_3	E	187–193	34[c]	EtOH	1640[d]	7.9

[a]Methods: A, alkylation of **1**; B, alkylation of **13**; C, alkylation of **21***g*; D, acid hydrolysis of **21***g*; E, see Experimental.
[b]Before recrystallization.
[c]Analytically pure.
[d]Nujol.
[e]$CHCl_3$.
[f]Conversion yield, pure.

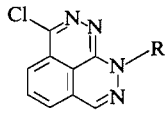
TABLE 5. 1-Substituted-1*H*-pyridazino[3,4,5-*de*]phthalazines

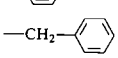
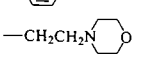


No.	R	Method[a]	Melting point (°C)	Yield (%)	Recrystallization solvent	^{1}Hmr (δ) (DMSO-d_6) H at C-3	H at C-7
22*a*	$-CH_3$	B C	149–151 147–149	71[c] 66[b]	EtOH	8.0	8.8
22*b*		B	168.5–170	50[c]	Benzene	8.3	9.1
22*c*		A	145–148	15[c]	EtOAc	8.15	9.0
22*d*		A	138–140	16[c]	Isopropanol	8.1	8.9
22*e*	$-CH_2CH_2CN$	A	203–206	24[c]	Benzene	8.2	9.0
22*f*	$-CH_2CH_2COOH$	D	251.5–253.5	35[c]	EtOH–H_2O	8.1	8.95
22*g*		A	117–121	18[c]	Hexane	8.1	8.95
22*h*		B	198–201	40[c]	EtOH	8.3	9.1
22*i*		A	160–161	22[c]	CH_3OH	8.05	8.9

[a]Methods: A, direct alkylation of **2**; B, dehalogenation of **18**; C, desulphurization of **19**; D, alkaline hydrolysis of **22***e*.
[b]Yield before recrystallization.
[c]Purified.

TABLE 6. 3-Chloro-9-substituted-9*H*-pyridazino[3,4,5-*de*]phthalazines



No.	R	Melting point (°C)	Yield (%)	Recrystallization solvent	^{1}Hmr (δ) (DMSO-d_6) H at C-7	Additional absorptions
18*a*	$-CH_3$	253–255	87[a] 48[b]	Ethanol	8.1	3.75 (s, CH_3), 7.6–8.0 (m, 3*H*, aryl)
18*b*		225–228	66[b]	Ethanol	8.4	7.45–8.3 (m, 8*H*, aryl)
18*c*		208–209	75[a] 38[b]	Benzene	8.1	5.35 (s, CH_2), 7.2–8.0 (m, 8*H*, aryl)
18*d*		257–258	92[a] 74[b]	2-Methoxyethanol	8.4	7.45–8.3 (m, 6*H*, 3 aryl + 3 pyridyl), 8.7 (dd, *H* at 6′)
18*e*		207–209	56[a]	Benzene	8.05	2.5 (m, 2CH_2), 2.8 (t, CH_2), 3.5 (m, 2CH_2), 4.3 (t, CH_2), 7.2–7.9 (m, 3*H*, aryl)

[a]Crude yield.
[b]Analytically pure.

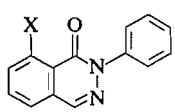
examples explored it appears that dehalogenation of **18** is the best route to these structures.

In the course of the work, we attempted to build structures **22** as we had done for **11**, in this case by generation of an aldehyde function in the 8-position of a 2-substituted 1(2*H*)-phthalazinone. Attempts to reduce esters or acid chloride functions at the 8-position to an aldehyde such as **23** or an alcohol such as **24** with metal hydrides by standard literature methods gave, at best, low yields of the expected product. In one instance, the reason for the poor yield was clear. Lithium borohydride, a

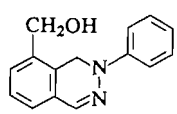
reagent not noted for reducing amides (26) reduced the ester **12***d* to the amino alcohol **25** when used in excess. This is reminiscent of the overreduction of esters and lactones with sodium borohydride in the work of Wenkert *et al.* (27) in which ready intramolecular hydride transfer to a neighbouring carbonyl group occurred from an intermediate obtained from a newly formed primary alcohol combined with excess borohydride. A similar rationale could account for the reduction product **25** and the poor yields in our other attempts.

Comparison of **22***a* (**22**: $R^1 = CH_3$) with **2** will serve to illustrate the significant changes in spectral properties caused by alkylation at the 1-position. The uv spectra are almost identical in neutral and acidic ethanol. The spectrum of **2** undergoes a bathochromic shift with base (1) whereas **22***a* remains unchanged. The broad ir absorption at 2800–2200 cm^{-1} in **2** is missing from the spectrum of **22***a* in Nujol. In the ^{1}Hmr spectra (DMSO-d_6), the low field exchangeable proton of **2** is replaced in **22***a* by a sharp singlet at 3.7 δ due to the *N*-methyl. The aromatic patterns and shifts are identical but the equivalent vinyl protons in **2** are replaced by singlets at 8.0 δ (H at C-3) and 8.8 δ (H at C-7) in **22***a*. The latter signal is missing in 7-substituted compounds such as **18**. The methanesulphonate of **2** shows a singlet corresponding to the two vinyl protons at 8.8 δ (D_2O) whereas **22***a* in DCl/D_2O shows separate singlets at 8.9 δ and 9.1 δ.

Reaction of **2** with methyl iodide or ethyl iodide gave stable quaternary salts, but when the methiodide was treated with freshly prepared silver oxide in aqueous methanol, a red solid was obtained, not identical to **22***a*. This red solid formed a yellow methiodide, mp 313–314°C, isomeric with the methiodide derived from **22***a*, mp 207–208.5°C. The methiodide of **22***a* showed ^{1}Hmr signals for methyls at 3.8 δ and 4.3 δ (DMSO-d_6) and proton singlets at 8.6 δ and 9.7 δ. Since the position of one methyl group is not in doubt, the lower melting methiodide must be structure **26** or, less likely due to steric

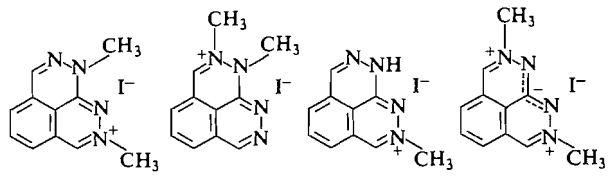


23 X = CHO
24 X = CH_2OH



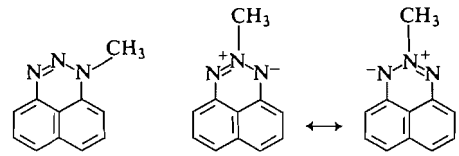
25

crowding, **27**. The higher melting methiodide showed equivalent methyl signals at 4.1 δ and a singlet corresponding to two identical vinyl protons at 9.0 δ with an aromatic multiplet centred at 8.0 δ. The spectrum indicates a molecule symmetrical about the C(5)—C(9b)—C(9a) axis. Assignment of structure **28** to the methiodide of **2** and structure **29**



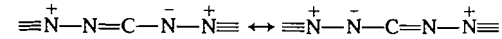
26 **27** **28** **29**

to the higher melting methiodide derived from **28** accounts for the observed spectral data. The ^{1}Hmr patterns of **26** and **28** are virtually identical except for the methyl singlet at 3.8 δ in **26** in place of the broad exchangeable singlet at 13.4 δ in **28**. These results are reminiscent of the two methylation products of 1*H*-naphtho[1,8-*de*]triazine, namely, the expected product **30** and the 2-methylated derivative **31** (28).



30 **31**

The unusual inner salt **29** is related to the aminimides (29, 30) except that the ammonium imine is stabilized in a



system contained in a flat molecule further stabilized by ring current.

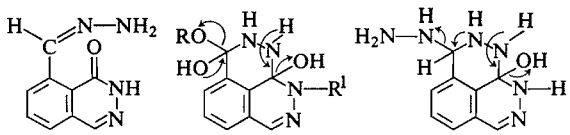
The relative ease with which the phthalazinone esters react with hydrazine to form the tricyclic system deserves comment, particularly in the examples where the nitrogen is substituted. One would not expect to prepare an amidrazone by reaction of an amide with hydrazine, especially a non-enolizable amide. If the reaction involved initial conversion of the ester to the hydrazide followed by intramolecular cyclization, we would have expected to isolate some bicyclic hydrazides, though admittedly we were not looking for them. The reaction of methylhydrazine with the acid chloride of **8** was designed to create a hydrazide in the first stage of the synthesis. This *enolizable* phthalazinone was ring closed only under vigorous conditions and not cleanly. The synthesis of the parent heterocycle **2**, attempted under a variety of conditions (1), suggests that the initial formation of the phthalazinone hydrazone **32** followed by intramolecular attack on the enolizable carbonyl of the phthalazinone moiety is not the major reaction pathway, since most ring closure methods resulted in either intermolecular azine formation or no reaction. Ring closure occurs in nonaqueous highly polar media only under forcing conditions to a

TABLE 7. Antihypertensive activity[a] of selected compounds

Test model	GPA 1595	GPA 2079	GPA 2265	GPA 3095	GPA 3166	1-Hydrazinophthalazine
Intact anaesthetized cat	3 iv	3 iv	1 id	3 id	3 id	
Renal hypertensive dog	1 po	3 po	Emesis at 20 po	20 po	10 po	10 po
Normotensive dog		20 po		Inactive 10–40 po		20 po
Normotensive anaesthetized dog			10 iv 20 id	Inactive at 30 id	3 id	30 id 1 iv
Neurogenic hypertensive dog				40 po	40 po	10 po
DOCA rat	100 po			Inactive at 100 po	40 po	5 po
Normotensive rat	30 po			Inactive at 300 po	100 po	30 po
Spontaneous hypertensive rat				80 po		
Normotensive cat			Emesis at 10 po			
Normotensive monkey			Emesis at 25 po			

[a]Key: Activity reported in mg/kg is the minimal dose tested which produced blood pressure lowering of at least 20%, but not necessarily the minimal effective dose. iv: intravenously; id: intraduodenally; po: orally.

small extent. On the other hand, dilute aqueous hydrazine at reflux was an excellent medium for conversion of **32** to the tricyclic system in good yield and purity. Since hydrazine is a strong nucleophile and the formation of the tricyclic system seems favoured by moderately high dilution in a hydroxylic solvent (water or water/alcohol mixtures) we suggest that the mechanism for the formation of **2** from **32** involves formation of a transient intermediate **34**, which stabilizes itself by



32 **33** **34**

elimination of hydrazine and water. Similarly, the formation of **11** from **10** involves formation of an intermediate such as **33** which undergoes a double elimination depicted by the arrows to form the highly resonance-stabilized tricyclic system. Furthermore, the distance between the carbonyl carbon atoms of **10** appears optimal for allowing nucleophilic attack by hydrazine to form **33** and subsequently **11**.

Biological results

Derivatives of the tricyclic system were tested for blood pressure lowering activity, primarily in the acute anaesthetized cat via intraduodenal administration. Secondary screening was done usually in the Goldblatt dog (31). Other models were also used in secondary screening.

Since **3**(*GPA 1595*) (1) was highly active, it was not surprising to find examples of structure **20** also active. The best of the three examples by far was **20***a*, coded as *GPA 2079*. This was highly active in the anaesthetized cat, Goldblatt dog, and the unanaesthetized normotensive dog. Since it was more toxic in mice than *GPA 1595*, it was not further pursued. Many of the 9-substituted derivatives of **1** lowered blood pressure in the anaesthetized cat. The first one to be studied in depth, **11***q* (*GPA 2265*), was also active in the anaesthetized dog but caused emesis in unanaesthetized dogs, cats, and monkeys. Most of the 9-pyridylalkyl compounds were active and the one most thoroughly investigated was **11***w* (*GPA 3166*). This compound was active in anaesthetized cats and dogs, the Goldblatt dog, the DOCA rat, and the neurogenic hypertensive dog (32) with no indication of tolerance on repeated dosage. The drug showed tachycardia in the anaesthetized animals and the Goldblatt dog, but not in the neurogenic dog which suggested that the tachycardia was reflex in origin. Lack of significant autonomic effects suggested a peripheral vasodilator mechanism of action. Further studies in toxicology and pharmacology revealed an unacceptable safety margin and the compound was not pursued clinically. The 9-alkyl and 9-aralkyl deriv-

atives of **1** were generally poorly active in the cat, except for the *trans*-cinnamyl derivative **11***k* (*GPA 3095*). This was moderately active in the anaesthetized cat, Goldblatt dog, neurogenic dog, and spontaneous hypertensive rat without tachycardia except slightly in the anaesthetized cat. It was inactive in the anaesthetized dog, DOCA rat, and normotensive rat. Even with micronized preparations, absorption was poor as determined by blood level studies in rats. Since pharmacological dose–response results were variable during repeated testing, possibly due to erratic absorption, the compound was not further investigated. The phthalazinone acids and esters were tested for antiinflammatory activity. The most promising of these, acid **12***j* (*GPA 3273*) was active in the anticarrageenin rat paw test with little ulcerogenic potential, but it failed in secondary screening in the 14-day established adjuvant arthritis screen. None of the compounds in Tables 4, 5, and 6 were sufficiently active in the primary screen to warrant further study.

Experimental

Melting points (uncorrected) were determined on a Thomas–Hoover capillary apparatus or, if above 250°C, on a Reichart hot stage apparatus. Infrared spectra (ir) reported in wave numbers (cm^{-1}) over the 3500–1500 cm^{-1} range for the principal peaks in Nujol (N) or chloroform ($CHCl_3$) were measured on a Perkin–Elmer model 137 calibrated with respect to the 1602 cm^{-1} band of polystyrene or on a model 457 grating instrument. Proton magnetic resonance spectra (^{1}Hmr) were measured on a Varian EM-390 spectrometer in DMSO-d_6 unless otherwise stated, with peaks reported in ppm relative to tetramethylsilane as internal standard. Ultraviolet spectra (uv) were recorded on a Cary 14B spectrophotometer in nanometers with ε values in parentheses. All new compounds had microanalytical data for C, H, and N fitting within ±0.3. Additional elements are reported.

*2-Methyl-1(2*H*)-phthalazinone (**16**)*

A mixture of phthalaldehydic acid (18 g) and glacial acetic acid (100 mL) was treated with methyl hydrazine (7.6 mL) and the whole stirred at reflux under nitrogen for 18 h. The resulting solution was concentrated to dryness under water vacuum and the residue taken up in methanol (30 mL), treated with water (30 mL), and refrigerated. After 15 h the precipitated solid was collected, washed with methanol, and air dried. The product (15.5 g, 81%, mp 111–113°C) was recrystallized from cyclohexane (800 mL) to afford pure white crystals, mp 111.5–113°C (14.0 g). Literature mp values: 116°C (20); 111–112°C (10); 105–108°C (14); 114°C (9a); 112–114°C (17, 19). Infrared (N) ν: 1637 (C=O) cm^{-1} (lit. (14) ν: 1645 cm^{-1}); ^{1}Hmr: 3.8 (s, CH_3), 7.8–8.5 (m, 4*H*, aryl), 8.5 (s, vinyl *H*); literature (20) values: 3.71 (s, 3*H*), 8.31 (s, *H*), 7.65–8.30 (m, 4*H*).

*Synthesis of 3-substituted-3,4-dihydro-4-oxophthalazine-5-carboxylic esters **10** (Table 2)*

*Method A. From **9** with alkyl halide/alcohol/aqueous sodium hydroxide*

Methyl 3,4-dihydro-4-oxo-5-phthalazine carboxylate (**9***a*, 2.04 g (1)) was suspended in a solution of methanol (20 mL) and methyl iodide (0.75 mL), treated with 4*N* aqueous sodium hydroxide (2.3 mL), and heated under reflux for 1 h. It was quenched in ice, extracted with benzene, and the benzene extract dried (Na_2SO_4) and concentrated to dryness at reduced pressure. The residual solid (1.9 g, mp 113–119°C) was recrystallized from water to constant mp (3 recrystallizations) to afford pure **10***a*, mp 125–126°C; ir ($CHCl_3$): 1740, 1650, 1595; ^{1}Hmr: 3.65 (s, CH_3—), 3.85 (s, CH_3—), 7.75–8.2 (m, 3*H*, aryl), 8.5 (s, vinyl *H*).

*Method B. From **12** via the acid chloride*

3-Methyl-3,4-dihydro-4-oxo-5-phthalazine carboxylic acid (**12***a*, 52 g) was suspended in a mixture of thionyl chloride (125 mL) and chlorobenzene (550 mL) and heated 3 h at reflux. The mixture was cooled and the precipitate collected, washed with benzene, and air dried to give the acid chloride (28.3 g, mp 185–190°C). Evaporation of the filtrate and trituration of the residue with hexane gave a second crop (23.4 g, mp 182–186°C) suitable for the next step. The acid chloride (15 g) was stirred at reflux in absolute ethanol (300 mL) during 18 h, cooled, and the white solid collected, washed with ethanol, and dried to afford the pure ester **10***b* (7.8 g, mp 103–104.5°C); ir (N): 1730, 1650, 1595; ^{1}Hmr: 1.3 (t, CH_3—C), 3.8 (s, CH_3—N), 4.4 (q, CH_2), 7.8–8.15 (m, 3*H*, aryl), 8.6 (s, vinyl *H*).

*Method C. From **9** with an alkyl halide/sodium methoxide/dimethyl sulphoxide*

A mixture of methyl 3,4-dihydro-4-oxo-phthalazine-5-carboxylate (**9***a*, 40.8 g), sodium methoxide (12 g), and dimethylsulphoxide (300 mL) was treated dropwise under stirring with 3-chloropropenylbenzene (40 g) in dimethylsulphoxide (50 mL). The mixture was stirred at 80°C for 4 h under moisture exclusion and then quenched in ice and excess 2*N* HCl. The brownish solid was collected, washed with water, and extracted with chloroform. The dried (Na_2SO_4) extract was concentrated to dryness, taken up in a minimal quantity of hot methanol, treated with charcoal, and filtered. On cooling, pale yellow crystals (42.3 g, mp 116–121°C) were obtained. One crystallization from methanol and two from chloroform–hexane gave pure **10***h* as white crystals, mp 123–124°C; ir (N): 1730, 1650; ^{1}Hmr: 3.95 (s, CH_3—O), 4.95 (d, CH_2—, J = 5), 6.5 (dt, *CH*, J = 5, 16), 6.7 (d, *CH*, J = 16), 7.25–7.65 (m, 5*H*, benzene ring), 7.85–8.2 (m, 3*H*, aryl), 8.65 (s, vinyl *H*). The coupling constants indicate a *trans* double bond.

*Method D. From **9** with an alkyl halide/lithium amide/dimethylsulphoxide*

To a solution of methyl 3,4-dihydro-4-oxo-phthalazine-5-carboxylate (**9***a*, 40.8 g) in dry dimethylsulphoxide (100 mL) under nitrogen was added lithium amide (5 g) and the mixture stirred 2 h at ambient temperature. Additional lithium amide (5 g) was added followed by 2-picolyl chloride hydrochloride (32.8 g) portionwise. The resulting dark solution was stirred 3 h at ambient temperature under nitrogen, poured into water (1.5 L), and refrigerated 3 days. The precipitated product (35 g, mp 109–112°C) was dissolved in a minimal quantity of methanol, treated with an equimolar amount of methanesulphonic acid and the methanesulphonate salt of **10***l* purified by recrystallization from ethanol, mp 170.5–173°C; ir (N) ν: 1660, 1735 (C=O); ^{1}Hmr: 2.55 (s, CH_3—S), 3.9 (s, CH_3O), 5.75 (s, CH_2), 7.8–9.1 (m, 7*H*, aryl + pyridyl), 8.65 (s, vinyl *H*), 14.95 (s, O*H*, exchangeable in D_2O).

*Ethyl-3,4-dihydro-4-oxo-phthalazine-5-carboxylate (**9**b)*

To a vigorously stirred solution of thionyl chloride (40 mL) in chlorobenzene (200 mL) was added 3,4-dihydro-4-oxo-phthalazine-5-carboxylic acid (1) (30.4 g) and the whole heated 4 h at reflux under moisture exclusion. The solid was collected on a ground glass filter, washed with benzene, pressed dry, and then transferred to a round bottom 1 L flask containing absolute

ethanol (305 mL). The mixture was heated at reflux under moisture exclusion 18 h, treated hot with activated charcoal, and filtered. On cooling, off-white crystals were obtained (26.1 g, mp 170–171.5°C) identical to the product obtained by a different route (1) as shown by ir, ^{1}Hmr, and mmp.

Synthesis of 3-substituted-3,4-dihydro-4-oxo-5-phthalazinone carboxylic acids **12** *(Table 1)*

Method A. From 3-hydroxyphthalide-7-carboxylic acid and a monosubstituted hydrazine

A mixture of phenylhydrazine (3.6 mL), 3-hydroxyphthalide-7-carboxylic acid (1) (5.82 g), and glacial acetic acid (100 mL) was stirred 18 h at reflux, concentrated to dryness at reduced pressure, triturated with cold methanol, and collected. The crude acid **12***b* (6.97 g, mp 197–199°C) was recrystallized from benzene to afford pure white crystals, mp 197–198°C; ir (N): 2680, 1705, 1665, 1590; ^{1}Hmr: 7.4–7.85 (m, 5*H*, phenyl), 7.9–8.25 (m, 3*H*, aryl), 8.7 (s, vinyl *H*), 13.4 (s, O*H*).

Method B. From 3-hydroxyphthalide-7-carboxylic acid and a substituted hydrazine salt

To a stirring solution of *p*-fluorophenylhydrazine hydrochloride (18 g), anhydrous sodium acetate (14.2 g), and glacial acetic acid (1.3 L) was added 3-hydroxyphthalide-7-carboxylic acid (19.4 g) and the mixture stirred 18 h at reflux. The mixture was filtered hot and the filtrate concentrated to one-third volume at reduced pressure and diluted with water. The resulting precipitate (24.2 g, mp 228–234°C) was twice recrystallized from ethyl acetate to afford pure white crystals of **12***c*, mp 234–237°C; ir (N): ~2600, 1695, 1655, 1585; ^{1}Hmr: 7.3–8.2 (m, 7*H*, aryl), 8.7 (s, vinyl *H*), 13.3 (s, O*H*). *Anal.* calcd. for $C_{15}H_9N_2O_3F$: F 6.69; found: F 6.63.

Method C. By hydrolysis of **10**

A mixture of methyl 3-phenylpropyl-3,4-dihydro-4-oxo-phthalazine-5-carboxylate (**10***m*, 33 g, bp 225°C/2 Torr, prepared from **9***a*) and 2 *N* sodium hydroxide (500 mL) was stirred at reflux for 3 h, cooled, and poured into water (2.5 L). The mixture was extracted with chloroform and the aqueous layer was evaporated at reduced pressure to one-third volume and acidified with 6 *N* HCl under cooling. The mixture was extracted with chloroform, the chloroform layer dried (Na_2SO_4), and the material obtained as an oil by evaporation of the solvent at reduced pressure. It was stirred in ethanol at −8°C for 12 h and the solid which formed (**12***i*, 19.7 g, mp 110–112°C) was recrystallized once from methanol and once from benzene–hexane to afford the pure acid (14.2 g), mp 115–117°C; ir (N): ~1910, 1690; ^{1}Hmr: 2.15 (m, C*H*$_2$), 2.6 (q, C*H*$_2$, *J* = 7), 4.2 (t, C*H*$_2$, *J* = 7), 7.25–7.45 (m, 5*H*, phenyl), 7.8–8.15 (m, 3*H*, aryl), 8.6 (s, vinyl *H*), 13.35 (s, O*H*).

*Synthesis of 9-substituted-3-oxo-3*H*-2,9-dihydropyridazino-[3,4,5-*de*]phthalazines* **11** *(Table 3)*

Method A. From **10**

A mixture of methyl 3-methyl-3,4-dihydro-4-oxophthalazine-5-carboxylate (**10***a*, 95.3 g), hydrazine hydrate (1650 mL), and water (400 mL) was stirred at reflux for 66 h. The mixture was allowed to cool to room temperature and 9-methyl-3-oxo-3*H*-2,9-dihydropyridazino[3,4,5-*de*]phthalazine (**11***a*) was collected, washed with water, and oven dried at reduced pressure. The bright yellow crystals (84 g, mp 292–296°C, 96% yield) were unchanged on recrystallization from 2-methoxyethanol; ir (N): 3130, 1650, 1595, 1555; uv (MeOH, neutral): 218 (21 600), 273.5 (8 900), 299.5 (8 000), 311.0 (7 000), 374.0 (6 000); (MeOH, acid): 253.0 (5 900), 263.0 (6 200), 273.5 (5 900), 300.0 (7 200), 312.0 (7 300), 331.0 (4 700), 364.0 (4 900); ^{1}Hmr: 3.55 (s, C*H*$_3$), 7.8 (s, *H* at C-7), 7.7–8.1 (m, 3*H*, aryl), 12.1 (s, N*H*).

Method B. From **12**

A mixture of 3-(4-pyridylethyl)-3,4-dihydro-4-oxo-phthalazine-5-carboxylic acid (**12***m*, 64.5 g), thionyl chloride (90 mL), and chlorobenzene (650 mL) was stirred 3 h at reflux under moisture exclusion and then concentrated to dryness at reduced pressure. The residue was treated with absolute methanol (2 L) at reflux for 18 h and then concentrated at reduced pressure to a yellow foam. This material was treated with hydrazine hydrate (800 mL), water (200 mL), and then methanol (300 mL) to produce a homogenous solution. It was heated under stirring and the liquid gradually allowed to distil off at a bath temperature of 130°C. After a further 66 h at this temperature, the mixture was cooled and the yellow solid collected (44 g), washed with water, and then dissolved as well as possible in excess 1 *N* HCl. After filtration to remove 4.4 g of **1**, the solution was made basic with 5% sodium carbonate and the precipitated solid was collected, washed with water, air dried, and recrystallized thrice from ethanol to afford pure **11***z*, mp 200.5–203°C; ^{1}Hmr: 3.1 (t, C*H*$_2$, *J* = 5), 4.3 (t, C*H*$_2$, *J* = 5), 7.3 (m, 2 C*H*—C), 7.9 (s, *H* at C-7), 7.75–8.2 (m, 3*H*, aryl), 8.5 (m, 2 C*H*—N), 12.0 (s, N*H*). The free base suspended in warm methanol was treated with an equimolar quantity of methanesulphonic acid, treated with ether to turbidity, refrigerated 90 h, and the *methanesulphonate salt* collected, mp 253–256°C, resolidified and dec. ca. 340°C; ir (KBr): ~2900 (broad), 1660, 1638, 1620, 1600, 1560, 1520, 1503. *Anal.* calcd. for $C_{16}H_{13}N_5O\cdot CH_4O_3S$: S 8.28; found: S 8.28.

Method C. From **9**

To a solution of 1 *N* sodium hydroxide (100 mL) in methanol (100 mL) was added *N*-hexamethyleneiminoethyl chloride hydrochloride (20 g) and the resulting mixture added to a solution of methyl 3,4-dihydro-4-oxophthalazine-5-carboxylate (**9***a*, 20.4 g) in methanol (250 mL). Additional 1 *N* sodium hydroxide (100 mL) was added and the whole heated 3 h on a steam bath. It was evaporated to dryness at reduced pressure and the residue triturated with water, extracted with chloroform, and the dried (Na_2SO_4) extract concentrated at reduced pressure to a brown oil. This was treated with hydrazine hydrate (420 mL) and water (140 mL) at reflux over 48 h, well cooled, and the precipitate collected, washed with water, and oven dried. The crude yellow solid was triturated with excess 1 *N* HCl, filtered free of impurities, and the filtrate made basic with 20% sodium carbonate solution. The yellow solid which formed was dissolved in chloroform, filtered free of further impurities, and concentrated at reduced pressure to a yellow solid (17.0 g, mp 182–185°C, 55%). Three recrystallizations from ethanol gave pure 3-(*N*-hexamethyleneiminoethyl)-3-oxo-3*H*-2,9-dihydropyridazino-[3,4,5-*de*]phthalazine (**11***t*), mp 183.5–186.5°C; ir(N): 3130, 1655, 1625, 1595. ^{1}Hmr: 1.5 (s, 4-C*H*$_2$), 2.5–2.95 (t + m, 3-C*H*$_2$—N), 4.1 (t, C*H*$_2$, *J* = 5), 7.95 (s, *H* at C-7), 7.75–8.15 (m, 3*H*, aryl), 12.0 (s, N*H*).

In examples **11***b*, **11***e*, **11***f*, **11***l*, **11***m*, and **11***x*, the crude solid obtained after hydrazine hydrate treatment was taken up in hot chloroform, filtered free of **1**, evaporated to dryness, and recrystallized. In examples **11***w*, **11***aa*, and **11***bb*, the crude tricyclic compound was converted to the methanesulphonate salt and recrystallized.

Method D. From **1**

To a suspension of sodium methoxide (7 g) in dry dimethylsulphoxide (500 mL) was added **1** (18.6 g) and the mixture heated to 60°C. Benzyl bromide (14 mL) was added under stirring and the mixture maintained 2 h at 60°C. The dark mixture was poured into ice water, stirred 0.5 h, and filtered. The dark precipitate was stirred 1 h in ethanol (400 mL) and the resulting tan solid (18.3 g) recrystallized from 2-methoxyethanol with charcoal. On cooling, a first crop (5.3 g) was obtained, combined with a second crop (4.1 g) obtained after 3 days, and recrystallized thrice from ethanol to afford pure 9-benzyl-3-oxo-2,9-dihydropyridazino[3,4,5-*de*]phthalazine (**11***h*), mp 239–243°C; ir (N):

3150, 1645, 1590, 1550; ^{1}Hmr: 5.2 (s, CH_2), 7.4 (s, C_6H_5), 8.05 (s, *H* at C-7), 7.85–8.2 (m, 3*H*, aryl), 11.9 (s, N*H*).

In examples **11***c*, **11***p*, **11***q*, and **11***y*, the crude product was dissolved in hot ethanol, filtered free of unreacted **1**, and concentrated to dryness before the final crystallization. In addition, **11***p* and **11***y* were dissolved in 1 *N* HCl, filtered free of impurity, and reprecipitated with aqueous sodium carbonate before the final recrystallization.

*3-Chloro-9-phenyl-9*H*-pyridazino[3,4,5-*de*]phthalazine (**18**b) (Table 6)*

To a stirring mixture of phosphorous pentachloride (6.3 g) in phosphoryl chloride (40 mL) was added 9-phenyl-3-oxo-3*H*-2,9-dihydropyridazino[3,4,5-*de*]phthalazine (**11***g*, 7.8 g) and the mixture stirred 3 h at reflux. It was poured cautiously onto ice, made alkaline with 20% sodium hydroxide solution, and the yellow precipitate collected and washed thoroughly with water. The crude solid was further triturated with warm water (600 mL), refiltered, and recrystallized from boiling ethanol to afford yellow crystals (5.5 g) of pure **18***b*, mp 225–228°C; ir (N): 1620, 1595, 1530. *Anal.* calcd. for $C_{15}H_9ClN_4$: Cl 12.63; found: Cl 12.67.

In example **18***c*, the reaction mixture was quenched instead in ice-cold ether, filtered, and the precipitate recrystallized. In example **18***d*, phosphoryl chloride alone was used as the chlorinating agent. In example **18***c*, the crude product was extracted from the ice-water mixture with chloroform, concentrated, and filtered through a column of Woelm neutral alumina, grade I, before final recrystallization.

*9-Phenyl-3-thiono-3*H*-2,9-dihydropyridazino[3,4,5-*de*]-phthalazine (**19**b)*

A mixture of phosphorous pentasulphide (2.5 g), dry pyridine (15 mL), and **11***g* (2.6 g) was stirred at reflux under moisture exclusion for 2.5 h. The dark red solution was cooled, poured into ice-cold saturated sodium chloride solution, and stirred 1.5 h. The precipitated thiono compound was collected, washed thoroughly with water, air dried, and recrystallized from ethanol in golden yellow flakes, mp 230–231°C; ir (N): 3150, ~2400 (broad), 1615, 1590, 1560; ^{1}Hmr: 7.4–8.25 (m, 7*H*, phenyl + aryl), 8.3 (s, *H* at C-7), 8.6 (dd, *H* at C-4), 13.8 (s, N*H*). *Anal.* calcd. for $C_{15}H_{10}N_4S$: S 11.52; found: S 11.64.

The *9-methyl compound* **19***a*, prepared by the same route, was obtained in 56% yield after one recrystallization from 2-methoxyethanol. Two further recrystallizations did not change the mp of 299–316°C (dec.); ir (N): ~3180, ~2800 (broad), 1620, 1555, 1520; ^{1}Hmr: 3.6 (s, CH_3), 8.05 (s, *H* at C-7), 7.8–8.15 (2*H*, aryl), 8.45 (dd, *H* at C-4), 14.0 (s, N*H*). *Anal.* calcd. for $C_{10}H_8N_4S$: S 14.83; found: S 14.72.

*9-(*N*-Morpholinoethyl)-3-thiono-3*H*-2,9-dihydropyridazino-[3,4,5-*de*]phthalazine (**19**c)*

To a solution of **11***q* (29.9 g) in pyridine (250 mL) was added phosphorous pentasulphide (25 g) and the mixture stirred 5 h at reflux. The dark solution was poured into ice-water and the yellow solid collected, washed with water, and pressed dry on the filter. The crude product (15.5 g), mp 200–204°C dec., was suspended in hot chloroform (500 mL), filtered and the filtrate treated with hexane, whereupon a yellow precipitate formed. This material (6.6 g, one spot in tlc) was twice recrystallized from benzene to afford the pure thiono compound **19***c*, mp 202–204°C, resolidified, and remelted 220–222°C; ir (N): ~3150, 1590, 1555; ^{1}Hmr: 2.5 (m, 2CH_2), 2.7 (t, CH_2), 3.55 (m, 2CH_2), 4.15 (t, CH_2), 7.85–8.1 (m, 2*H*, aryl), 8.15 (s, *H* at C-7), 8.5 (dd, *H* at C-4), 13.9 (s, N*H*). *Anal.* calcd. for $C_{15}H_{17}N_5OS$: S 10.17; found: S 10.15.

*3-Hydrazino-9-methyl-9*H*-pyridazino[3,4,5-*de*]phthalazine (**20**a)*

To a hot stirring solution of hydrazine hydrate (162 mL) and water (60 mL) was added **19***a* (6.48 g) and the mixture stirred mechanically 20 h at reflux. It was filtered hot and the filtrate evaporated at reduced pressure to dryness. The residual yellow solid was taken up in 3 *N* HCl (400 mL), filtered to remove insoluble material, and the filtrate evaporated to dryness at reduced pressure. It was dissolved in water (100 mL), again filtered free of impurity, and the filtrate concentrated to dryness. The residual solid was dissolved in water (50 mL), ethanol (50 mL) added and, at 70°C under stirring, treated with benzaldehyde (15 mL) in ethanol (50 mL). Water (25 mL) was added, followed by 1 *N* sodium bicarbonate (100 mL), and the mixture stirred 5 min at 70°C. Bicarbonate solution (100 mL) was again added and the whole heated 10 min at reflux. The mixture was cooled and the orange solid collected, washed with water, and treated with excess 2 *N* HCl at the boil (fume hood) until no odour of benzaldehyde remained and a yellow solution was obtained. It was filtered through sintered glass and the clear yellow filtrate concentrated to dryness at reduced pressure. The residual solid was dried in a dessicator over P_2O_5 and recrystallized from methanol–ether to give pale yellow crystals of the dihydrochloride of **20***a* (4.4 g), mp ~260°C, gas evolution; ir (N): ~2600 (broad), 1580, 1545, 1510; ^{1}Hmr (D_2O): 4.05 (s, CH_3), 8.15–8.6 (m, 3*H*, aryl), 8.7 (s, *H* at C-7). *Anal.* calcd. for $C_{10}H_{10}N_6 \cdot 2HCl$: Cl 24.70; found: Cl 24.44.

In a similar way, **19***b* was reacted with aqueous hydrazine hydrate followed by benzaldehyde to afford the benzylidene hydrazone of *3-hydrazino-9-phenyl-9*H*-pyridazino[3,4,5-*de*]-phthalazine* in 63% yield, crude. After three recrystallizations from 2-methoxyethanol, it melted in the range 219–222°C; ir (N): 3350, 1615, 1590, 1565, 1550, 1530; ^{1}Hmr: 7.3–7.95 (m, 12*H*, aryl), 8.0 (s, *H* at C-7), 8.3 (dd, *H* at C-4, J = 7, 1.5), 8.4 (s, C*H*=N), 11.5 (s, N*H*).

*9-Benzyl-3-hydrazino-9*H*-pyridazino[3,4,5-*de*]phthalazine hydrochloride (**20**c) from **11**h*

A mixture of phosphorous pentasulphide (25 g), pyridine (250 mL), and **11***h* (28 g) was stirred 3 h at reflux. The dark mixture was poured into ice-water, stirred 2 h, and the precipitated solid collected and recrystallized from 2-methoxyethanol. The resulting product was suspended in chloroform, filtered, and 7 g of crude thiono compound obtained, mp 275–278°C. It was suspended in hydrazine hydrate (300 mL) and water (80 mL), stirred 20 h at reflux, well cooled, and the solid collected, washed with water, taken up in 3 *N* HCl (400 mL), and filtered. The filtrate was concentrated at reduced pressure and the residue recrystallized from methanol to afford the monohydrochloride of **20***c*, mp 270–271°C; ir (N): 3200, ~2800 (broad), 1650, 1585, 1545; ^{1}Hmr: 5.3 (s, CH_2), 7.2–7.5 (m, 5*H*, phenyl), 8.05–8.15 (m, 2*H*, aryl), 8.2 (s, *H* at C-7), 8.7 (dd, *H* at C-4). *Anal.* calcd. for $C_{16}H_{14}N_6 \cdot HCl$: Cl 10.81; found: Cl 10.92.

*2,9-Dimethyl-3-oxo-3*H*-2,9-dihydropyridazino[3,4,5-*de*]-phthalazine (**21**b)*

*(a) **21**b from **11**a*

To a suspension of **11***a* (20 g) in dimethylsulphoxide (200 mL) was added sodium methoxide (10 g) and the mixture stirred at 60°C. A thick yellow suspension formed. Methyl iodide (20 mL) was added whereupon the suspension became a clear yellow solution from which a yellow solid gradually precipitated. The mixture was stirred 3 h at 60°C, cooled, washed with dilute aqueous sodium bisulphite followed by water, and air dried. The yellow solid (20 g, mp 191–192°C, sint. 186°C) was recrystallized from methanol to give pure **21***a*, mp 195–196.5°C; ir ($CHCl_3$):

1650, 1625, 1595, 1555; uv (MeOH): 274.5 (8900), 301.0 (7100), 312.5 (6300), 374.0 (6700), unchanged in acidic or alkaline methanol; ^{1}Hmr: 3.5 (s, CH_3), 3.6 (s, CH_3), 7.85 (s, *H* at C-7), 7.6–8.05 (m, 3*H*, aryl); ^{1}Hmr ($CDCl_3$): 3.6 (s, CH_3), 3.8 (s, CH_3), 7.5–7.95 (m, 3*H* aryl + *H* at C-7), 8.25 (dd, *H* at C-4, J = 8, 1.5).

(b) ***21b*** *from* ***1***

In an apparatus consisting of a 4-necked flask, thermometer, dropping funnel, mechanical stirrer, and double jacketed condenser surmounted with a nitrogen T-tube, a suspension of **1** (56 g) in dimethylsulphoxide (700 mL) was treated under stirring with sodium methoxide (36 g), whereupon the internal temperature rose to 34°C. After the weak exotherm subsided, methyl iodide (15 g) was added, whereupon the internal temperature rose to 72°C. After stirring 2 h at ambient temperature, the mixture was poured into ice-water (700 mL) containing a little sodium bisulphite. It was made slightly acidic with HCl, stirred 30 min at 0–5°C, and filtered. The filtrate was extracted with chloroform (3 × 750 mL) and the extract dried (Na_2SO_4) and concentrated to dryness. The residual yellow solid (15.1 g), mp 186–189°C, was identical (ir, ^{1}Hmr) to **21***b* obtained from **13***a*. Evaporation of the aqueous dimethylsulphoxide layer to dryness followed by extraction with chloroform containing 5% methanol yielded a mixture of **21***b* and **13***a* (10.8 g).

*2,9-Bis-(*N*-morpholinoethyl)-3-oxo-3*H*-2,9-dihydropyridazino-[3,4,5-*de*]phthalazine (**21f**) from* ***1***

To a suspension of **1** (93 g) in dimethylsulphoxide (600 mL) was added sodium methoxide (29 g) and the mixture raised to 80°C under stirring. *N*-Morpholinoethyl chloride (75 g) was added and the mixture stirred 5 h longer at 80°C, quenched in ice-water (3 L), and the yellow precipitate collected. The wet solid (ca. 100 g) was impure **11***q*. The mother liquor was extracted with chloroform and the organic layer extracted with 2*N* HCl. The acidic layer was made basic with 5% sodium carbonate solution and extracted with chloroform. The dried (Na_2SO_4) organic layer was concentrated to 20 g of dark semisolid. It was taken up in a minimum quantity of ethyl acetate and chromatographed on Woelm basic alumina, grade III (400 g), with ethyl acetate as eluent. The second 500 mL fraction, on evaporation at reduced pressure, gave a yellow solid. Recrystallization from ethyl acetate gave pure **21***f* (2.2 g), mp 179–182°C; ir (N): 1645, 1620, 1595, 1540; ^{1}Hmr: 2.5 (m, 4CH_2), 2.75 (t, 2CH_2), 3.55 (m, 4CH_2), 4.2 (2 overlapping dd, 2CH_2), 7.95 (s, *H* at C-7), 7.75–8.2 (m, 3*H*, aryl).

*2,9-Bis-(cyanoethyl)-3-oxo-3*H*-2,9-dihydropyridazino-[3,4,5-*de*]phthalazine (**21g**)*

A mixture of **1** (55.8 g), 50% aqueous pyridine (500 mL), Triton B (40% in CH_3OH, 10 mL), and acrylonitrile (60 mL) was heated 18 h at reflux. It was evaporated at reduced pressure to dryness, taken up in water (700 mL), filtered, and the precipitate (80.4 g, mp 186–192°C) recrystallized three times from ethanol (ca. 40 mL/g) to afford the pure sample, mp 188–191.5°C; ir (N): 2220, 1645, 1590, 1545; ^{1}Hmr: 3.1 (q, 2CH_2), 4.3 (m, 2CH_2), 8.05 (s, *H* at C-7), 7.8–8.25 (m, 3*H*, aryl).

*2,9-Bis-(1-methyl-2-cyanoethyl)-3-oxo-3*H*-2,9-dihydropyridazino[3,4,5-*de*]phthalazine (**21h**)*

A mixture of **1** (18.6 g), crotononitrile (20 mL), Triton B (3 mL), and 50% aqueous pyridine (1 L) was heated 18 h at reflux. The red solution was concentrated to dryness at reduced pressure and the residue triturated with water, cooled, and filtered. The solid was taken up in chloroform, filtered to remove residual **1** (6.5 g), and the filtrate concentrated to dryness at reduced pressure. The residue (14 g) was recrystallized from benzene–hexane with charcoal, then thrice from chloroform–ether to afford the pure product (5.6 g, 29% conversion), mp 168–170°C; ir (N): 2230, 1645, 1625, 1595, 1550; ^{1}Hmr: 1.5 (t, 2CH_3), 3.1 (2d, 2CH_2), 5.0–5.65 (m, 2C*H*), 8.0 (s, *H* at C-7), 7.9–8.35 (m, 3*H*, aryl).

*2,9-Bis-(carbamoylethyl)-3-oxo-3*H*-2,9-dihydropyridazino-[3,4,5-*de*]phthalazine (**21i**)*

A mixture of **21***g* (7.17 g) and 80% sulphuric acid (75 mL) was stirred for 20 h under reflux. The resulting yellow suspension was cooled and quenched in ice. The yellow precipitate (7.1 g, mp 230–235°C) was twice recrystallized from water to afford the pure product, mp 234–238°C; ir (N): 3350, 3150, 1650, 1620, 1575, 1530; ^{1}Hmr: 2.55 (m, 2CH_2), 4.25 (q, 2CH_2), 6.95 (s, NH_2), 7.5 (s, NH_2), 8.0 (s, *H* at C-7), 7.8–8.2 (m, 3*H*, aryl).

*9-Methyl-2-(*N*-morpholinoethyl)-3-oxo-3*H*-2,9-dihydropyridazino[3,4,5-*de*]phthalazine (**21c**)*

Sodium methoxide (2.5 g) was added to a stirring suspension of **11***a* (6 g) in dimethylsulphoxide (200 mL), heated to 80°C, *N*-(2-chloroethyl)morpholine (6 g) added, and the mixture stirred 5 h at 80°C. The orange solution was quenched in ice-water and extracted with chloroform. The organic layer was extracted with 1*N* HCl (500 mL) and the acidic layer made basic with 5% sodium carbonate, extracted with chloroform, dried (Na_2SO_4), and concentrated to dryness to give the crude product (9.3 g, mp 171–174°C). Three recrystallizations from benzene gave the pure sample, mp 176–179°C; ir (N): 1645, 1620, 1595, 1550; ^{1}Hmr: 2.5 (dd, 2CH_2, J = 5), 2.75 (t, CH_2, J = 7), 3.5 (s, CH_3), 3.6 (dd, 2CH_2, J = 5), 4.1 (t, CH_2, J = 7), 7.6–8.05 (m, 3*H*, aryl), 7.8 (s, *H* at C-7).

Under similar conditions, **21***d* was prepared from **11***g*, except that the crude product precipitated directly on quenching in ice-water and was obtained pure after three recrystallizations from isopropanol in 40% yield, mp 162–164.5°C; ir (N): 1645, 1620, 1595, 1550; ^{1}Hmr: 2.4 (dd, 2CH_2, J = 5), 2.6 (t, CH_2, J = 7), 3.5 (dd, 2CH_2, J = 5), 4.05 (t, CH_2, J = 7), 7.3–8.25 (m, 8*H*, aryl), 8.15 (s, *H* at C-7).

*2-Cyanoethyl-9-(*N*-morpholinoethyl)-3-oxo-3*H*-2,9-dihydro-[3,4,5-*de*]phthalazine (**21e**)*

A mixture of **21***g* (12.0 g), dimethylsulphoxide (300 mL), and sodium methoxide was heated to 60°C under stirring and *N*-(2-chloroethyl)morpholine (10 g) added. It was stirred 4 h at 60°C under moisture exclusion, then poured into ice-water. The resulting solid (7.1 g) was suspended in 1*N* HCl, filtered and the filtrate made basic with 5% sodium carbonate solution, extracted with chloroform and the chloroform layer concentrated to dryness at reduced pressure. The residual solid (5.5 g) was recrystallized from methanol to produce the pure **21***e* (3.45 g), mp 195–198°C; ir (N): 2220, 1650, 1615, 1590, 1545; ^{1}Hmr: 2.5 (m, 2CH_2), 2.7 (t, CH_2, J = 7), 3.05 (t, CH_2, J = 7), 3.6 (m, 2CH_2), 4.2 (t, CH_2, J = 7), 4.3 (t, CH_2, J = 7), 8.05 (s, *H* at C-7), 7.8–8.25 (m, 3*H*, aryl).

Preparation of ***11q*** *from* ***21e***

A mixture of **21***e* (1.3 g), hydrazine hydrate (30 mL), and water (7 mL) was stirred 20 h at reflux. It was cooled and the yellow precipitate collected, washed with water, and dried. The product (0.8 g, mp 200–203°C) was recrystallized from water to afford 0.6 g, mp 203–205°C, identical by ir, ^{1}Hmr, and mmp to **11***q* prepared from **1**.

*2-Methyl-3-oxo-3*H*-2,9-dihydropyridazino[3,4,5-*de*]-phthalazine (**21a**)*

The acid chloride of 3,4-dihydro-4-oxo-phthalazine-5-carboxylic acid, prepared as described in the synthesis of **9***b* (40 g)

was suspended in chlorobenzene (250 mL) and methylhydrazine (50 mL) added cautiously. The mixture was stirred at reflux 44 h under moisture exclusion, cooled in an ice bath, and treated cautiously with methanol (200 mL). The crude solid (12.8 g, mp ~300°C dec.) was collected and combined with a second batch (17.3 g) and suspended in 50% aqueous pyridine (900 mL). Acrylonitrile (25 mL) and Triton B (5 mL) were added and the mixture stirred 18 h at reflux. The orange solution was concentrated to dryness at reduced pressure and the residue triturated with water and collected. The crude product (15.2 g) was twice recrystallized from ethanol to afford *9-cyanoethyl-2-methyl-3-oxo-3*H-*2,9-dihydro[3,4,5-*de*]phthalazine* (**21***j*), mp 187–193°C; ir (N) v: 2220 (C≡N), 1640 (C=O); ^{1}Hmr: 3.1 (t, CH_2, J = 7), 3.65 (s, CH_3), 4.2 (t, CH_2, J = 7), 7.9 (s, *H* at C-7), 7.7–8.1 (m, 3*H*, aryl). The nitrile **21***j* (7.6 g) was treated with hydrazine hydrate (240 mL) and water (60 mL) under reflux for 18 h, cooled in ice, and the yellow precipitate collected, washed with water, and dried. The product **21***a* was thus obtained analytically pure, mp 307–311°C dec.; ir (N): 3200 (sh), 3100, 1655, 1630, 1605, 1590, 1550; ^{1}Hmr: 3.6 (s, CH_3), 7.85 (s, *H* at C-7), 7.65–8.05 (m, 3*H*, aryl), 12.1 (s, N*H*).

*1-Methyl-1*H-*pyridazino[3,4,5-*de*]phthalazine* (**22**a)

Method A. From **18**a

A mixture of **18***a* (10.8 g), 47% hydriodic acid (150 mL), and red phosphorous (10 g) was stirred at reflux for 23 h, poured into ice-water, and filtered. The filtrate was evaporated to a small volume at reduced pressure, made basic with 5% sodium carbonate solution, and extracted with chloroform. The chloroform layer was dried (Na_2SO_4), concentrated to a small volume, and chromatographed on Woelm neutral alumina, grade II, in a 2 inch diameter column. The desired compound fluoresced strongly under long wave (3660 Å) uv light and its progress down the column was determined with a Rayteck model LS-7 handheld lamp. After a forerun, the compound was eluted with chloroform (ca. 2 L). Evaporation of the chloroform left 9.3 g of yellow solid, which was combined with a second run (8.0 g) and recrystallized from ethanol with charcoal to afford pure **22***a* (13.1 g), mp 149–151°C; ir (N): 1615, 1590, 1535; uv (MeOH, neutral or alkaline): 254.0 (6 700), 332.2 (11 400), 341.5 (11 500); uv (MeOH + 0.1 *N* HCl): 2445 (9 300), 253.0 (8 400), 312.5 (9 500), 334.5 (5 900), 348.8 (6 000); ^{1}Hmr: 3.7 (s, CH_3), 7.45–7.9 (m, 3*H*, aryl), 8.0 (s, *H* at C-3), 8.85 (s, *H* at C-7); ^{1}Hmr (DCl/D_2O): 4.1 (s, CH_3), 8.3–8.65 (m, 3*H*, aryl), 8.9 (s, vinyl *H*), 9.1 (s, vinyl *H*).

Method B. From **19**a

The thiono compound **19***a* (1.08 g) was suspended in ethanol (200 mL) and Raney nickel slurried in ethanol (ca. 5 g) added a little at a time as the mixture was agitated with an air-driven stirrer. After addition was complete, the whole was stirred on a steam bath for 1 h. It was filtered hot and the filtrate evaporated at reduced pressure. The residual solid was again dissolved in hot ethanol, refiltered, and concentrated to dryness. The residual yellow solid (0.6 g) was recrystallized from benzene–hexane with charcoal to give 0.4 g of product, mp 147–149°C, identical to **22***a* derived from **18***a* as indicated by tlc, ir, and ^{1}Hmr. This substance formed a hydriodide with 47% hydriodic acid, mp 247–248°C dec. (from ethanol–ether); ir (N): ~2700 (broad), 1640, 1580, 1570.

Treatment of **22***a* with methanol and methyl iodide at reflux over 25 h gave a methiodide **29**, mp 207–208.5°C (from methanol–ether); ir (N): 1615, 1595, 1550; ^{1}Hmr: 3.8 (s, CH_3), 4.3 (s, CH_3), 8.1–8.5 (m, 3*H*, aryl), 8.6 (s, *H* at C-3), 9.7 (s, *H* at C-7).

*1-Phenyl-1H-pyridazino[3,4,5-*de*]phthalazine* (**22**b)

A mixture of red phosphorous (6.5 g), 47% hydriodic acid (65 mL), and **18***b* (9.0 g) was stirred 18 h at reflux, poured into ice-water, and filtered. The filtrate was made basic with 5% sodium carbonate and extracted with chloroform. The extract was dried (Na_2SO_4) and concentrated to dryness at reduced pressure. The residual crude product (6.5 g) was recrystallized from benzene with charcoal and a first crop of 3.1 g obtained. Addition of hexane to the mother liquor gave an additional 0.7 g. The combined material was recrystallized from benzene to give pure **22***b* (2.9 g), mp 168.5–170°C; ir (N): 1600, 1575, 1520; uv (MeOH, neutral or alkaline): 343.2 (13 400); uv (MeOH + 0.1 *N* HCl): 311.7 (9 900), 336.5 (6 400), 351.0 (7 000); ^{1}Hmr: 7.4–8.1 (m, 8*H*, aryl), 8.3 (*H* at C-3), 9.1 (*H* at C-7).

Method C. From **2**

*1-(*N-*Morpholinoethyl)-1*H-*pyridazino[3,4,5-*de*]phthalazine* (**22**d)

Sodium methoxide (1.7 g) was added to a suspension of **2** (5.1 g) in dimethylsulphoxide (75 mL), the mixture stirred at 60°C, and *N*-(2-chloroethyl)morpholine (5 g) added under moisture exclusion. After 4 h stirring at 80°C, the red solution was poured into ice-water and extracted with chloroform. The extract was washed with 1 *N* HCl and the aqueous acid layer made basic with 5% sodium carbonate and extracted with chloroform. Evaporation of the dried (Na_2SO_4) chloroform yielded 6 g of dark semisolid. This was dissolved in a minimal quantity of 5:1 benzene–dimethylformamide and chromatographed on Woelm neutral alumina, grade I (200 g). The first 150 mL fraction, on evaporation, yielded a yellow solid (3 g, mp 131–135°C). This was combined with material from a second run (6 g) and recrystallized from ethanol with charcoal. The product (7.5 g) was again recrystallized from ethanol and twice from isopropanol to afford the pure sample (4.0 g, 16%), mp 138–140°C; ir (N): 1630, 1605, 1545; ^{1}Hmr: 2.5 (m, 2CH_2), 2.75 (t, CH_2, J = 7), 3.55 (m, 2CH_2), 4.35 (t, CH_2, J = 7), 7.5–8.0 (m, 3*H*, aryl), 8.1 (s, *H* at C-3), 8.9 (s, *H* at C-7).

*1-(2-Pyridyl)-1*H-*pyridazino[3,4,5-*de*]phthalazine* (**22**h)

A mixture of **18***d* (11.24 g), red phosphorous (8 g), and 47% hydriodic acid (100 mL) was stirred 3 h at reflux, cooled, poured into ice-water, and extracted with chloroform. The dried (Na_2SO_4) extract was concentrated to dryness and the residual solid (9.7 g, mp 182–188°C) chromatographed on Woelm basic alumina, grade I (500 g), with chloroform as eluent. The eluted product (6.4 g) was recrystallized twice from ethanol to afford the pure compound, mp 198–201°C, in 40% yield; ir (KBr): 1620, 1585, 1565, 1540; ^{1}Hmr: 7.5–8.2 (m, 6*H*, 3 aryl + 3 pyridyl), 8.3 (s, *H* at C-3), 8.8 (m, *H* at C-6 in pyridyl ring), 9.1 (s, *H* at C-7).

The free base was treated with an equimolar amount of methanesulphonic acid in methanol, concentrated to dryness at reduced pressure, taken up in water, filtered, and the filtrate concentrated to dryness. The residual solid was twice recrystallized from isopropanol to afford the methanesulphonate salt of **22***h*, mp 186–189°C; ir (KBr): 1640, 1610, 1595, 1570, 1520. *Anal.* calcd. for $C_{15}H_{13}N_5O_3S$: S 9.34; found: S 9.21.

*1-(*N-*Hexamethyleneiminoethyl)-1*H-*pyridazino[3,4,5-*de*]-phthalazine* (**22**g)

To a suspension of **2** (8.5 g) in methanol (200 mL) was added *N*-(2-chloroethyl)hexamethyleneimine hydrochloride (9.9 g) in methanol (100 mL) followed by 1 *N* sodium hydroxide (100 mL). It was stirred 3 h at reflux and then evaporated to dryness at reduced pressure. The dark residue was chromatographed in 5:1 benzene–dimethylformamide on Woelm neutral alumina, grade I, with 100 mL fractions eluted. The second fraction yielded 5.2 g of yellow solid, which was recrystallized from benzene (20 mL) – hexane (300 mL) with charcoal to afford pure **22***g*, mp 117–121°C; ir (N): 1620, 1600, 1535; ^{1}Hmr: 1.55 (s, 4CH_2), 2.7 (m, 2CH_2—N), 2.9 (t, CH_2, J = 7), 4.3 (t, CH_2, J = 7), 7.55–8.05 (m, 3*H*, aryl), 8.1 (s, *H* at C-3), 8.95 (s, *H* at C-7).

By the same method, *1*-trans-*cinnamyl-1*H-*pyridazino[3,4,5-de]phthalazine* was obtained after chromatography in a crude yield of 35%, mp 135–140°C. It was twice recrystallized from ethanol to afford pure **22***c*, mp 147–149°C; ir (N): 1620, 1595, 1530; ^{1}Hmr: 4.95 (d, CH_2, J = 5), 6.6 (dt, C*H*, J = 5, 16), 6.8 (d, C*H*, J = 16), 7.25–8.05 (m, 8*H*, aryl), 8.15 (s, *H* at C-3), 9.0 (s, *H* at C-7).

*1-(2-Pyridylethyl)-1*H-*pyridazino[3,4,5-de]phthalazine (22i)*

A mixture of **2** (8.5 g), 2-vinylpyridine (20 mL), glacial acetic acid (125 mL), and anhydrous cupric sulphate (50 mg) was stirred 4 h at 135–140°C, then evaporated to dryness at 100°C/12 Torr. The residue was triturated with water, well cooled, and the crude product (6.6 g, mp 150–153°C) twice recrystallized from methanol with charcoal to afford pure **22***i*, mp 160–161°C; ir (N): 1620, 1590, 1565, 1540; ^{1}Hmr: 3.3 (dd, CH_2, J = 9, 7.5), 4.6 (dd, CH_2, J = 9, 7.5), 7.2–7.9 (m, 6*H*, aryl + 3 pyridyl), 8.05 (s, *H* at C-3), 8.55 (dd, *H* at C-6), 8.9 (s, *H* at C-7).

*1-(2-Cyanoethyl)-1*H-*pyridazino[3,4,5-de]phthalazine (22e)*

A mixture of **2** (10.2 g), Triton B (2 mL), acrylonitrile (12 mL), and 50% aqueous pyridine (500 mL) was stirred at reflux for 1 h, concentrated to dryness at reduced pressure, triturated with water, and filtered. The residual solid (10.1 g, mp 195–197°C) was combined with 5.1 g from a one-half scale run, dissolved largely in 400 mL of chloroform, filtered, and the chloroform solution treated with hexane (800 mL) and cooled. The precipitate which formed (12.3 g, mp 197–199°C) was chromatographed on Woelm neutral alumina, grade I (450 g), with ethyl acetate as eluent. After removal of an impurity with 1 L of solvent, acetone was used as eluent and 500 mL fractions taken. Fractions 4 to 7 were combined, concentrated to dryness, and recrystallized from benzene to give pure **22***e* (4.8 g), mp 203–206°C; ir (N): 2250, 1620, 1600, 1540; ^{1}Hmr: 3.15 (t, CH_2, J = 7), 4.5 (t, CH_2, J = 7), 7.45–8.05 (m, 3*H*, aryl), 8.2 (s, *H* at C-3), 8.9 (s, *H* at C-7).

*1-(2-Carboxyethyl)-1*H-*pyridazino[3,4,5-de]phthalazine (22f)*

A mixture of **22***e* (11.15 g) and 10% sodium hydroxide (200 mL) was heated 1 h at reflux. The yellow solution was cooled, acidified to pH 4 with 6 *N* HCl, and the crystalline product which formed (9.7 g, mp 245–247°C) was recrystallized twice from wet ethanol to afford **22***f* (4.2 g), mp 251.5–253.5°C; ir (N): 3300, ~2400 (broad), ~1900 (broad), 1715, 1615, 1595, 1520; ^{1}Hmr: 2.8 (t, CH_2, J = 7.5), 4.4 (t, CH_2, J = 7.5), 7.55–8.0 (m, 3*H*, aryl), 8.1 (s, *H* at C-3), 8.95 (s, *H* at C-7), *OH* of carboxyl not visible.

*8-Hydroxymethyl-2-phenyl-1(2*H*)phthalazinone (24)*

The ester **10***c* (5.9 g) suspended in diglyme (15 mL) was treated portionwise with lithium borohydride (0.6 g) in diglyme (20 mL), the whole heated 4 h at 70°C, cooled, and treated cautiously with water. A pale off-white solid precipitated (4.2 g). It was recrystallized once from methanol and twice from benzene to afford colourless needles, mp 178–180°C; ir ($CHCl_3$): 3450, 1635, 1580; ^{1}Hmr: 5.15–5.5 (m, CH_2, O*H*), 7.45–7.7 (m, 5*H*, phenyl), 7.7–8.3 (3*H*, aryl), 8.6 (s, vinyl *H*).

When the reaction was carried out with twice the amount of lithium borohydride at 70°C for 6 h, work-up yielded 4.1 g of solid. Two recrystallizations from methanol gave 2.66 g of *8-hydroxymethyl-2-phenyl-1,2-dihydrophthalazine (25)*, mp 122–124°C; ir (N): 3280, 3180, 1595, 1560; ^{1}Hmr: 4.6 (d, CH_2—O, J = 6), 4.9 (s, CH_2 at C-1), 5.3 (t, O*H*), 6.9–7.5 (m, 8*H*, aryl), 8.55 (s, *H* at C-3).

Phenylhydrazone of 23

To a stirring solution of phenylhydrazine (25 mL) in ethanol (100 mL) was added 3-hydroxyphthalide-7-carboxaldehyde (**1**) (3.56 g) and the mixture heated 22 h at reflux. After 1.5 h, a yellow precipitate formed. The mixture was cooled to room temperature and the solid collected, washed thoroughly with ethanol, and twice recrystallized from 2-methoxyethanol to give the pure phenylhydrazone of *8-formyl-2-phenyl-1(2*H*)-phthalazinone* (4.77 g, 70%), mp 264°C; ir (N): 3250, 1645, 1600, 1550, 1530; ^{1}Hmr: 6.8–8.7 (m, 13*H*, aryl + *H* at C-4), 9.65 (s, —C*H*=N on C-8), 10.8 (s, N*H*).

Methanesulphonate of 2

Treatment of **2** with an equimolar amount of methanesulphonic acid in methanol followed by ether gave the salt, mp 288–293°C dec., after two recrystallizations from dimethylformamide; ir (N): 3280, ~2600 (broad), 1635, 1600, 1500; ^{1}Hmr (D_2O): 2.9 (s, CH_3—S), 8.1–8.5 (m, 3*H*, aryl), 8.8 (s, protons at C-3 and C-7). *Anal.* calcd. for $C_{10}H_{10}N_4O_3S$: S 12.04; found: S 11.96.

Methiodide of 2 (28)

A mixture of **2** (5.1 g), methyl iodide (16 mL), and methanol (200 mL) was stirred at reflux under moisture exclusion for 16 h. It was concentrated to dryness at reduced pressure and recrystallized from methanol. This product (5.23 g, mp 269–270.5°C) was twice recrystallized from methanol to yield pure methiodide, mp 279–281°C; ir (N): 1640, 1610, 1585, 1510; ^{1}Hmr: 4.3 (s, CH_3), 8.15–8.5 (m, 3*H*, aryl), 8.6 (s, C*H*=N—), 9.85 (s, C*H*=$\overset{+}{\text{N}}$=), 13.4 (s, N*H*). *Anal.* calcd. for $C_{10}H_{10}N_4I$: I 40.66; found: I 40.63.

In a similar way, the *ethiodide* was prepared in 60% crude yield and purified by two recrystallizations from ethanol, mp 260–262°C; ir (N): 1640, 1610, 1585, 1510; ^{1}Hmr: 1.6 (t, CH_3, J = 7), 4.5 (q, CH_2, J = 7), 8.1–8.5 (m, 3*H*, aryl), 8.6 (s, C*H*=N—), 9.8 (s, C*H*=$\overset{+}{\text{N}}$=), 13.6 (s, N*H*). *Anal.* calcd. for $C_{11}H_{11}N_4I$: I 38.91; found: I 39.02.

Conversion of 28 to 29

Silver nitrate (1.7 g) was dissolved in a minimal quantity of water, treated with 1 *N* sodium hydroxide (10 mL) and then quickly with **28** (3.12 g) dissolved in warm methanol (200 mL). The mixture was stirred at 65°C for 20 min and the dark brown mixture filtered. The filtrate was concentrated to dryness at reduced pressure to a dark red solid. This was taken up in hot chloroform, filtered, and the filtrate evaporated at reduced pressure to a brick red solid, mp ~190°C dec. A portion of this (460 mg) was suspended in methanol (35 mL), treated with methyl iodide (2 mL), and the whole refluxed 32 h under moisture exclusion. The mixture was cooled and filtered and the orange-yellow crystals collected (151 mg), mp 312–315°C dec. The methiodide was recrystallized from dimethylformamide to afford orange-yellow needles, mp 313–314°C dec.; ir (N): ~2500 (broad), 1610, 1580, 1540; ^{1}Hmr: 4.1 (s, 2CH_3), 7.9–8.25 (m, 3*H*, aryl), 9.1 (s, 2C*H*=$\overset{+}{\text{N}}$=). *Anal.* calcd. for $C_{11}H_{11}N_4I$: I 38.91; found: I 38.78.

5-Carboxy-3,4-dihydro-2-methyl-4-oxophthalazinium hydroxide, inner salt (17)

A mixture of **9***a* (41 g), methyl *p*-toluenesulphonate (35 mL), and chlorobenzene (100 mL) was heated under nitrogen at reflux for 18 h, more chlorobenzene added (150 mL), and reflux continued another 30 h. The mixture was filtered hot and the white precipitate collected, washed with chlorobenzene, then cyclohexane, and oven dried under vacuum at 120°C. The *p-toluenesulphonate salt of 17* (66 g, 84%), mp 205–207°C, was analytically pure; ir (N): ~2400 (broad), 1725, 1590, 1570, 1505; ^{1}Hmr: 2.3 (s, CH_3), 3.95 (s, CH_3), 4.4 (s, CH_3), 7.4 (q, 4*H*, aryl, 1,4-substituted), 8.25–8.65 (m, 3*H*, aryl), 10.2 (s, C*H*=$\overset{+}{\text{N}}$=), 14.6 (s, O*H*).

The tosylate (7.3 g) in warm water (200 mL) was treated dropwise with 2 *N* sodium hydroxide (10 mL). Zinc acetate dihydrate (2.2 g) in water (20 mL) was added, the whole evaporated at reduced pressure at 70°C to ca. 20 mL, and methanol

(240 mL) added. Some solid (0.6 g) formed at once and a second crop (1.6 g) was obtained after overnight refrigeration. The combined material was recrystallized from water to afford colourless plates (1.45 g) which, after drying at 85°C/0.1 Torr for 20 h, gave pure product, mp 302–305°C dec.; ir (N): 1730, 1610, 1550; ^{1}Hmr: 3.8 (s, CH_3O), 4.1 (s, $CH_3\overset{+}{N}$), 7.5–7.9 (m, 3*H*, aryl), 8.8 (s, $CH—\overset{+}{N}\equiv$).

Additional spectral data

^{1}Hmr of ***11j*** (DMSO-d_6): 2.1 (m, CH_2), 2.65 (t, CH_2), 4.0 (t, CH_2), 7.3 (s, C_6H_5), 7.95 (s, *H* at C-7), 7.75–8.2 (m, 2*H*, aryl), 11.9 (N*H*); ($CDCl_3$): 2.25 (m, CH_2), 2.8 (t, CH_2), 4.05 (t, CH_2), 7.25 (s, C_6H_5), 7.75 (s, *H* at C-7), 7.55–8.0 (m, 2*H*, aryl), 8.35 (dd, *H* at C-4, J = 8, 1.5), 11.4 (N*H*).

Acknowledgements

The authors are grateful to Mr. A. Clemente and Dr. P. Nicolson for microanalytical data, to Mr. D. Spiegel for uv studies, to Mrs. L. Raabis for ^{1}Hmr spectra, and to Miss C. Signor and Miss L. Samoyedna for ir spectra. The cardiovascular test results were supplied by Drs. S. J. Ehrreich, R. Lee, M. Antonaccio, and R. Tanz, anti-inflammatory tests by Mrs. M. L. Graeme, the toxicology results by Dr. R. Katz, and the absorption studies by Dr. G. Lucas. We also thank Dr. R. Rodebaugh for helpful discussions related to the ^{1}Hmr data.

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