9. Condensed Heterotricycles. Synthesis and Reactions of *b*-Fused 1(2*H*)-Isoquinolinones with Unusual Enaminic Properties[1])

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Homophthalic acid (**1**) undergoes reaction with 1,2-, 1,3-, and 1,4-diamines to give condensed 1(2*H*)-isoquinolinones like **2**, **4**, **13**, and **25** which exhibit marked enamine character. These are attacked by electrophiles at the N or C terminus. Some notable reactions of imidazoisoquinolone **2** are those with maleic and acrylic acids to form the tetracycles **48** and **51**, respectively. With propiolic acid, **5** underwent an interesting reaction to form the benzimidazonaphthyridine **53**. An equally interesting behaviour was elicited from **2** in its reaction with formaldehyde, when in addition to the expected methylene-bridged molecule **59**, the novel spiro derivative **60** was formed by the dimerisation of a presumed azadiene intermediate **63**.

1. Introduction. – Condensed 1(2*H*)-isoquinolinone systems of type **2** have been synthesized by the reaction of diamines with homophthalic acid (**1**) [1–3], homophthalic anhydride [4], or *o*-cyanomethylbenzoic acid [5] [6]. Diverse biological properties such as antiinflammation and analgesia have been claimed for these compounds [2] [3]. Their chemical profile has not been investigated widely, except for our initial observations on their marked enaminic character [1]. These compounds are formally ketene aminals, but since one of the basic N-atoms is acylated, they are heterocyclic enamines for which few parallels are available in enamine literature [7–11]. Pursuing our earlier chemistry [1], we have enlarged the scope of our synthesis to encompass many new tricyclic and tetracyclic systems and uncovered many interesting reactions, noteworthy among which are those of the imidazoisoquinolinone **2** with propiolic acid and formaldehyde to form **53** and **60**, respectively. We publish in this full paper details of syntheses and reactions of these condensed isocarbostyrils.

2. Syntheses. – Condensation of homophthalic acid (**1**) with 2 mol-equiv. of ethylenediamine in *o*-dichlorobenzene under reflux for 6 h gave 2,3-dihydroimidazo[1,2-*b*]isoquinolin-5(1*H*)-one (**2**) in 91% yield *(Scheme 1)*.

Structure **2** was favoured over the alternative imine structure **2a** on the basis of spectral data: ^{1}H-NMR ((D$_6$)DMSO): 3.58 (*t* with fine structure, 2 H–C(2)); 4.13 (*t* with fine structure, 2H–C(3)); 5.55 (*s*, H–C(10)); 6.70 (br. *s*, NH); 6.80–7.60 (*m*, H–C(7), H–C(8), H–C(9)); 8.00 (*d* with fine structure, H–C(6)); treatment of the solution with D$_2$O for 17 h led to disappearance of signals at 5.55 and 6.70 ppm. IR (nujol): 3220, 1680, 1630, 1590 cm^{-1}. UV (EtOH): 231 (4.48), 292 (infl. 4.18), 300 (4.26), 368 (3.60) nm. As expected for enamines [7], protonation

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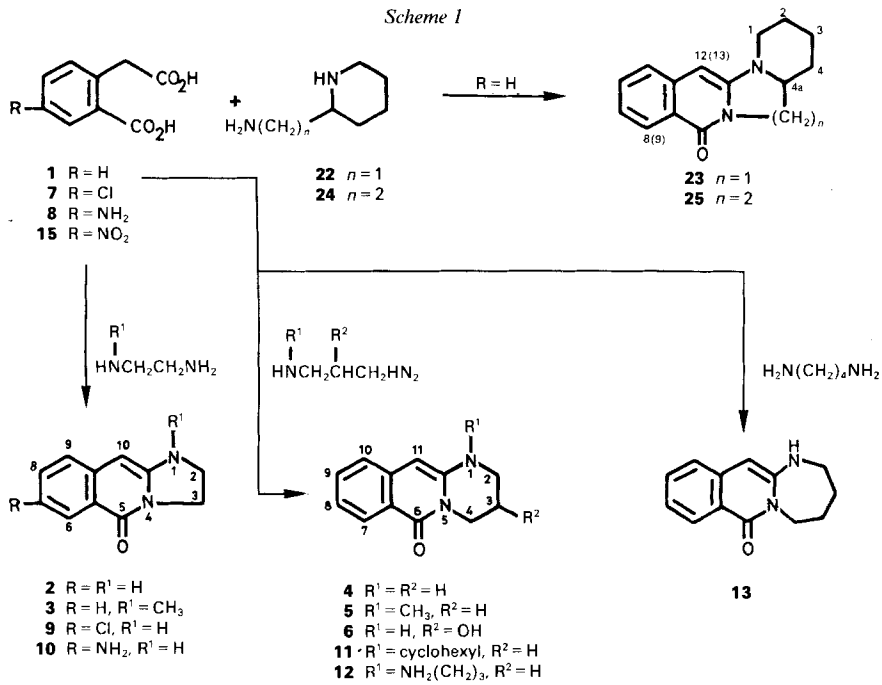
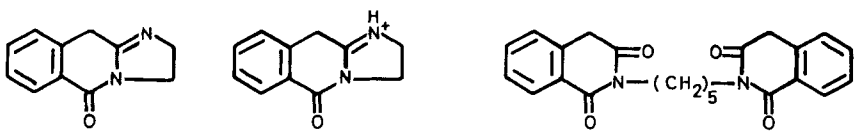
Scheme 1



of **2** occurred to produce salts with the iminium structure **2b**: ^{1}H-NMR (CF_3COOH): 4.50 (*m*, 2 H–C(2), 2 H–C(3)); 4.67 (br. *s*, 2 H–C(10)); 7.40–8.00 (*m*, H–C(7), H–C(8), H–C(9)); 8.23 (br. *d*, H–C(6)); 10.42 (br. *s*, NH^+). IR (nujol; chloride): 1730, 1670, 1640 cm^{-1}. UV (2N HCl): 233 (3.99), 240 (3.97), 264 (4.08) nm.

The condensation of homophthalic acid with *N*-methylethylenediamine, propane-1,3-diamine and its *N*-methyl as well as 2-hydroxy derivatives and of 4-chlorohomophthalic acid (**7**) and 4-aminohomophthalic acid (**8**) with ethylenediamine proceeded in high yields to afford fused 1(2*H*)-isoquinolinones **3**, **4**, **5**, **6**, **9**, and **10**, respectively. Yields of condensation were considerably less (42%), when *N*-cyclohexyl (→**11**) and *N*-(3-aminopropyl)propane-1,3-diamine (→**12**) were used with **1**. The yield of condensed isocarbostyril **13** using **1** and butane-1,4-diamine dropped to 21%, while with pentane-1,5-diamine, the only product isolated in scanty yield (8%) was the bis[homophthalimide] **14**.



2a **2b** **14**

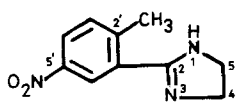
In their ^{1}H-NMR spectra, the enamine proton of the fused 1(2*H*)-isoquinolinones **3**–**6** and **9**–**13** appeared at 5.55±0.35 ppm. Their UV spectra (MeOH) exhibited characteristic maxima around 308±8 and 365±10 nm which were replaced by one at *ca.* 260 nm in 2N HCl. Other physical data are presented in *Table 1*.

Table 1. *Fused 1(2H)-Isoquinolinones* **2–6** *and* **9–13**

Compound No.	Yield [%]	Crystallized from	M.p. [°]	IR [cm^{-1}]	Molecular formula	Molecular weight	Analysis calc./found [%]		
							C	H	N
2	91	$CHCl_3$	210–211	3220, 1680, 1630, 1590	$C_{11}H_{10}N_2O$	186.21	70.95 71.16	5.41 5.74	15.05 14.89
2 · HCl		$EtOH/Et_2O$	230 (dec.)	1730, 1670, 1640	$C_{11}H_{11}ClN_2O$	222.68	59.33 59.60	4.98 5.29	12.58 12.84
2 · TsOH		$MeOH/Et_2O$	192–193	1680, 1650, 1590	$C_{18}H_{18}N_2O_4S$	358.34	60.33 60.54	5.06 5.34	7.82 7.95
3	90	aq. EtOH	162–163	1650, 1620, 1590	$C_{12}H_{12}N_2O$	200.23	71.98 71.57	6.04 6.29	13.99 14.25
3 · TsOH		$EtOH/Et_2O$	143–146		$C_{19}H_{20}N_2O_4S$	372.37	61.28 61.14	5.41 5.56	7.52 7.92
4	90	EtOH	170–171	3370, 1670, 1620, 1580	$C_{12}H_{12}N_2O$	200.23	71.98 71.78	6.04 6.00	13.99 13.91
5	88	aq. EtOH	130–131	1630, 1600, 1570	$C_{13}H_{14}N_2O$	214.26	72.87 72.68	6.59 6.72	13.08 13.29
5 · TsOH		$EtOH/Et_2O$	156–158	3530, 3470, 1700, 1690, 1620	$C_{20}H_{22}N_2O_4S$	386.39	62.16 62.44	5.74 5.82	7.25 7.20
6	90	aq. DMF	237–239	3340, 3200, 1640, 1610, 1580	$C_{12}H_{12}N_2O_2$	216.23	66.65 66.69	5.59 5.93	12.96 12.67
6 · TsOH		$MeOH/Et_2O$	195–197	3310, 1720, 1680, 1600	$C_{19}H_{20}N_2O_5S$	388.37	58.76 59.09	5.19 5.30	7.21 7.04
9	94	$CHCl_3$/EtOH	234–235	3260, 1660, 1600, 1580	$C_{11}H_9ClN_2O$	220.66	59.87 60.09	4.11 4.36	12.70 12.49
10	90	$CHCl_3$	250–251		$C_{11}H_{11}N_3O$	201.22	65.67 65.30	5.51 5.74	20.88 20.68
10 · HCl		MeOH	> 300	3320, 1630, 1600	$C_{11}H_{12}ClN_3O$	237.67	55.58 55.63	5.09 5.19	17.68 17.46
11	42	i-PrOH	129–130	1650, 1620, 1580	$C_{18}H_{22}N_2O$	282.37	76.56 76.14	7.85 8.08	9.92 9.61
11 · TsOH		$EtOH/Et_2O$	192–194	3400, 1730, 1620, 1600	$C_{25}H_{30}N_2O_4S \cdot H_2O$	472.52	63.54 64.05	6.83 6.65	5.92 6.02
12 · $(TsOH)_2$	42	MeOH/EtOH	214–216		$C_{29}H_{35}N_3O_7S_2 \cdot H_2O$	619.35	56.20 56.11	6.02 6.66	6.78 7.07
13	21	EtOH	151–153	3320, 1650, 1630, 1590	$C_{13}H_{14}N_2O$	214.26	72.87 72.90	6.59 6.90	13.08 13.37

The 4-nitrohomophthalic acid (**15**) and ethylenediamine afforded, under the usual conditions, the imidazole **16** in 25% yield. The structure rested on analytical and ^{1}H-NMR data (*s* at 2.55 ppm for CH_3Ar). Presumably, the formation of **16** is triggered by base-induced decarboxylation of the *p*-nitrophenyl-acetate ion followed by imidazoline formation at the surviving carboxylic centre.

The formation of condensed 1(2*H*)-isoquinolinones of the type **17** by reaction of homophthalic acid (**1**) with 2-aminoethanol and 2-aminoethanthiol was not observed in refluxing *o*-dichlorobenzene, although other reaction conditions have afforded them [2] [5]. Instead, we isolated only the homophthalimides **18** and **19** in yields of 50 and 19%, respectively. Semicarbazide and **1** could conceivably give **20**, but the product obtained by us in 32% yield was the *N,N'*-bi[homophthalimide] **21** ($C_{18}H_{12}N_2O_4$, M^+ 320), formed presumably from the initially produced *N*-ureidohomophthalimide *via* *N*-amino-homophthalimide (loss of HCNO).



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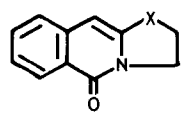
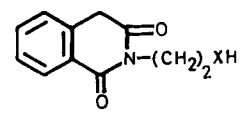
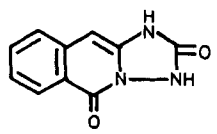


17 X = O or S



18 X = O
19 X = S



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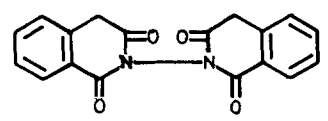

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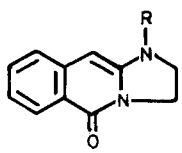
The facile formation of condensed 1(2*H*)-isoquinolinones from homophthalic acid could be exploited to construct tetracyclic systems. Thus, **1** and 2-(aminomethyl)-piperidine (**22**) afforded **23** in 14% yield *(Scheme 1)*. The yield of the homologue **25** rose to 85% using 2-(2-aminoethyl)piperidine (**24**). Structures **23** and **25** were supported by the presence of the typical signal due to the enaminic proton in their ^{1}H-NMR spectra (5.25 and 5.62 ppm, resp.).

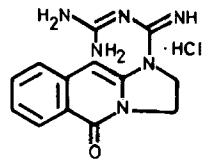
3. Reactions of Condensed 1(2*H*)-Isoquinolinones. – 3.1. *At N-Terminus.* Compound **2** was used as substrate for all reactions described in this section. Reaction of **2** with acid chloride or anhydride afforded generally the N-derivative, as revealed by the absence of NH absorption in the IR spectrum and presence in the ^{1}H-NMR spectrum of a *s* due to the enaminic proton at C(10) at 6.80–7.00 ppm (see **26–28**). Products with alkyl, aryl, and sulfonyl isocyanates are formulated similarly, as also those from sulfonyl chlorides (see **29–34**). Unlike reaction with classical enamines, methanesulfonyl chloride and **2** in the presence of Et_3N did not afford the cycloaddition product with methylenesulfene [7] [8]; only the 'normal' derivative **29** was formed. The yields of products **26–34** were moderate, except with butylisocyanate and 3,4,5-trimethoxybenzoyl chloride which gave only low yields *(Table 2)*. Careful workup of the crude mixture from the reaction of **2** with benzoyl chloride afforded, in addition to the colourless *N*-benzoyl derivative **27** as the major product (6.9 ppm (H–C(10)), a minor isomer, the 10-benzoyl derivative **35** (8.55 ppm

Table 2. N-*Acyl*, N-*Sulfonyl, and* N-*Carbamoyl Derivatives of* **2**

Compound No.	Yield [%]	Crystallized from	M.p. [°]	IR [cm^{-1}]	Molecular formula	Molecular weight	Analysis calc./found [%]		
							C	H	N
26	52	$CHCl_3$/hexane	235–236	1700, 1640, 1620	$C_{13}H_{12}N_2O_2$	228.24	68.41	5.30	12.27
							68.22	5.22	12.35
27	55	CH_2Cl_2/Et_2O	178–180	1670, 1660, 1605, 1590	$C_{18}H_{14}N_2O_2$	290.31	74.47	4.86	9.65
							74.72	5.04	9.72
28	5	$CHCl_3$	270–271	1660, 1620, 1600	$C_{21}H_{20}N_2O_5$	380.39	66.30	5.30	7.37
							66.45	5.61	7.35
29	56	EtOH	171–173	1650, 1600	$C_{12}H_{12}N_2O_3S$	264.23	54.54	4.58	10.60
							54.71	4.52	10.73
30	25	CH_2Cl_2/Et_2O	195–198	1650, 1630, 1600	$C_{18}H_{16}N_2O_3S$	340.32	63.52	4.74	8.23
							63.60	4.76	8.25
31	36	$CHCl_3$/EtOH	230–232	3300, 1660, 1640, 1600	$C_{13}H_{13}N_3O_2$	243.26	64.18	5.39	17.28
							63.98	5.66	16.93
32	10	EtOH	142–143	3500, 3400, 3280, 1670, 1640, 1580	$C_{16}H_{19}N_3O_2$	285.34	67.34	6.71	14.73
							67.07	7.24	14.37
33	44	dioxane	242–243	3300, 1690, 1640, 1620, 1600	$C_{18}H_{14}ClN_3O_2$	339.78	63.62	4.15	12.37
							63.40	4.38	12.48
34	74	pyridine	223–225	3380, 1640, 1600	$C_{19}H_{17}N_3O_4S$	383.35	59.53	4.47	10.96
							59.28	4.53	10.69



26 R = CH_3CO
27 R = PhCO
28 R = 3,4,5-$(MeO)_3C_6H_2CO$
29 R = CH_3SO_2
30 R = 4-$CH_3 \cdot C_6H_4 \cdot SO_2$
31 R = CH_3NHCO
32 R = BuNHCO
33 R = 4-ClC_6H_4NHCO
34 R = 4-$CH_3C_6H_4SO_2NHCO$



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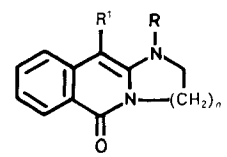


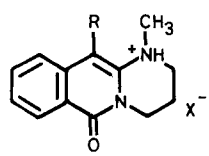
35 R = H, R^1 = PhCO; $n = 1$
36 R = H, R^1 = 4-$CH_3C_6H_4SO_2$; $n = 1$

38 R = H, R^1 = $PhCH_2$; $n = 1$
39 R = H, R^1 = $CH_2CH{=}CH_2$; $n = 1$

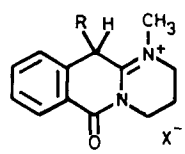
44 R = CH_3, R^1 = $PhCH_2$; $n = 2$
52 R = H, R^1 = CH_2CH_2CN; $n = 1$

(NH); 3320 cm^{-1}). Obviously, the *N*-benzoyl product reported earlier [4] is a mixture **27**/**35**. *p*-Toluenesulfonyl chloride also gave, in addition to **30** (6.70 ppm (H–C(10)), the *C*-sulfonyl isomer **36** (7.85 ppm (NH); 3380 cm^{-1}). The *N*-acyl derivatives of **2** were also differentiated generally from the C(10) derivatives with respect to the signals due to protons at C(2) and C(3) in the ^{1}H-NMR spectra: in the former, these were pseudo-*s* centered at *ca.* 4 ppm, while in the latter, they presented a frank A_2B_2 pattern centered at *ca.* 4.1 ppm. Reaction of **2** with *p*-nitrobenzenesulfonyl chloride gave a C(10) derivative discussed in *3.2.2.* While **2** was unreactive in the form of its hydrochloride towards KOCN and cyanamide, dicyandiamide gave **37**. Its poor solubility in NMR solvents precluded spectroscopic confirmation of the site of attack.

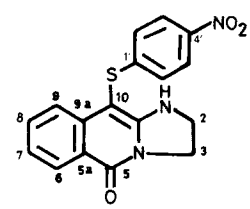
3.2 *Reactions at C-Terminus.* 3.2.1. *Alkylations.* Imidazoisoquinolinone **2** was unaffected by benzyl and allyl bromides in refluxing THF, but in the presence of K_2CO_3 **2** afforded derivatives **38** and **39** substituted at C(10) in 72 and 25% yield, respectively, as



40 R = CH_3; X = I
41 R = $PhCH_2$; X = Br



42 R = CH_3; X = I
43 R = $PhCH_2$; X = Br



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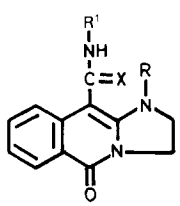
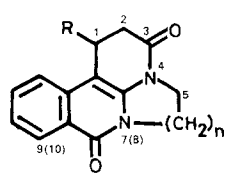
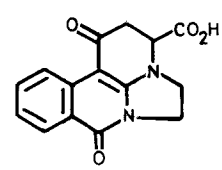


46 R = H, R^1 = Ph; X = S
47 R = Me, R^1 = 4-ClC_6H_4; X = O



48 R = CO_2H; $n = 1$
50 R = CO_2H; $n = 2$
51 R = H; $n = 1$



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shown by the IR (NH at *ca.* 3250 cm^{-1}) and ^{1}H-NMR data (no H–C(10)). Treatment of 1-methylpyrimidoisoquinolinone **5** with MeI and benzyl bromide afforded again the 11-substituted products as the salts (^{1}H-NMR: no enamine H–C(11)). The methyl derivative could have either of the structures **40** or **42**, and the benzylated product **41** or **43**. The ^{1}H-NMR spectra showed that **42** and **41** were predominating (*ca.* 70%).

In the ^{1}H-NMR ((D_6)DMSO) of **42** (*ca.* 70%), CH_3–C(11) appeared as *d* at 1.62 ppm (J = 7 Hz), H–C(11) as *q* at 5.03 ppm (J = 7 Hz), and CH_3–N^+ as *s* at 3.70 ppm. The relevant signals for species **40** could not be located in the midst of other signals. The ^{1}H-NMR (D_2O) of the benzyl product showed a *s* at 4.60 ppm for CH_2–C(11) of **41** (70%). The presence of the second species **43** was indicated by the presence of a *t* (J = 5 Hz) for H–C(11) at 5.20 ppm. These conflicting observations may in part be explained as being due to the use of different solvents; unfortunately, the solvents could not be switched, because of poor solubility of the substances in these solvents.

The base from the hydrobromide salt of the benzyl derivative could be liberated quantitatively. Its NMR spectrum was in total accordance with the expected structure **44** (CH_2–C(11) as *s* at 4.15 ppm). Surprisingly, **38** was a weak base and could not be induced to give a stable HCl or HI salt, although its UV spectra in MeOH and 2N HCl strongly resembled those of **2**.

Attempts to bridge the N- and C-termini of **2** with dichloroacetone and 1,3-dibromopropane were unsuccessful.

3.2.2. *Reaction with* p-*Nitrobenzenesulfonyl Chloride.* Interaction of **2** with this reagent in the presence of Et_3N gave, in 10% yield, a product formulated as the 10-(*p*-nitrophenyl)thio derivative **45**.

The IR spectrum (KBr) showed an NH band at 3450 cm^{-1}; the strong band due to the symmetric stretching of an SO_2 group was lacking at 1120–1160 cm^{-1}. ^{1}H- (400 MHz) and ^{13}C-NMR spectra (100.6 MHz) are also fully compatible with structure **45**, as evidenced by the chemical shifts given in the *Exper. Part.* The FD-MS showed mainly a M^+ signal at *m/z* 339 with only a small signal at *m/z* 371 which is likely to be due to an impurity (sulfone). In addition to this last impurity, the EI-MS exhibited the M^+ signal at *m/z* 339 and a prominent fragment ion at *m/z* 217, corresponding to the loss of the nitrophenyl radical. A pronounced metastable peak (*m/z ca.* 139) confirmed the direct genesis of the *m/z* 217 fragment ion from M^+. High-resolution MS gave the correct composition of M^+ as $C_{17}H_{13}N_3O_3S$ (found 339.0677; calc. 339.0677) and of the major fragment as $C_{11}H_9N_2OS$ (found 217.0453; calc. 217.0435).

The anomalous formation of **45**, albeit in very low yield, has no parallel to our knowledge in enamine literature. It could possibly arise from the primary 10-sulfonyl derivative by an intermolecular reduction/oxidation process.

Deliberate attempts to dehydrogenate **2** to the 2,3-didehydro derivative using nitrobenzene or Pd/C were unsuccessful.

3.2.3. *Reaction with Isothiocyanate and Isocyanate.* In contrast to phenylisocyanate, phenylisothiocyanate attacked **2** at C(10) to afford **46** in 42% yield (^{1}H-NMR: no H–C(10)). The 1-methyl derivative **3** is necessarily vulnerable at C(10) towards electrophilic reagents. However, it was unreactive towards many reagents studied – methanesulfonyl chloride and methyl- and phenylisocyanates. With *p*-chlorophenylisocyanate, however, the expected product **47** was obtained in 37% yield.

3.2.4. *Reactions with Electron-Deficient Olefins.* The marked enaminic properties of **2** were discovered accidentally when a maleate salt was sought to be prepared thereof. Heating an equimolar mixture of **2** and maleic acid in EtOH for ½ h resulted in the formation of the tetracyclic lactam **48** in 70% yield.

The structure was supported, besides by elemental analysis, by the absence of ^{1}H-NMR signals of the enaminic proton and of the vinyl protons of maleic acid, and by the IR spectrum (no band due to NH; bands at 1710, 1700

and 1680 cm^{-1} due to C=O). The alternative formulation **49** was ruled out since the ^{1}H-NMR showed the presence of only *one* aromatic proton at low field (8.20 ppm).

Maleic acid and **4** gave similarly **50**, although only in 15% yield. Acrylic acid reacted likewise with **2** to form the tetracycle **51**; acrylonitrile and **2**, on the other hand, gave only the 10-cyanoethyl derivative **52** (IR: CN band; ^{1}H-NMR: no H–C(10)).

We then studied the reaction of **2** with propiolic acid in the hope of preparing a didehydro derivative of **51**. The reaction was carried out with an excess of the acid in EtOH under reflux for 10 h. The yellow product obtained in *ca.* 80% yield was neither the simple adduct nor the resultant, expected lactam. From the analytical and spectral data, structure **53** could be unambiguously deduced.

Analytical and MS data pointed to a molecular formula $C_{26}H_{24}N_4O_2$. The IR spectrum had bands at 3380, 1680, 1620, and 1590 cm^{-1}. The UV spectrum (MeOH) showed the presence of *two* units per molecule of the chromophore present in **2**. The 400-MHz ^{1}H-NMR spectrum of a saturated solution in $CDCl_3$ (*Fig. 1*) showed

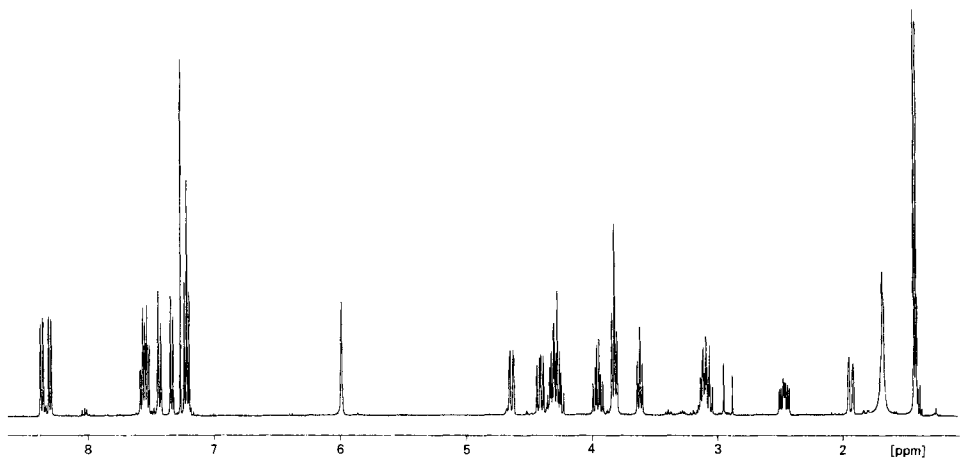


Fig. 1. *400-MHz ^{1}H-NMR spectrum of* **53** *in $CDCl_3$* (10 mg/ml). The signals at 7.26 and 1.70 ppm stem from $CHCl_3$ and H_2O. The signal at 6.0 ppm corresponds to an NH.

Table 3. *^{13}C- and ^{1}H-NMR Chemical Shifts of* **53**[a])

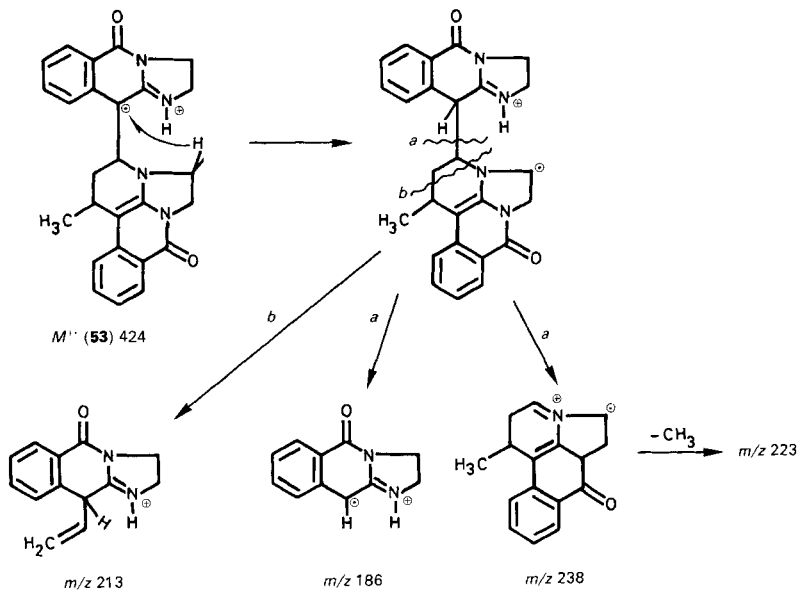
C/H	δ_C	δ_H	C/H	δ_C	δ_H
C(5)	160.60	–	H–C(8a) or H–C(5'a)	121.08	–
C(8)	160.17	–	H–C(12)	120.65	7.31
C(10'a)	144.97	–	H–C(9')	118.79	7.42
C(12c)	143.07	–	C(12b)	94.43	–
C(9'a)	138.43	–	C(10')	86.67	–
C(12a)	138.10	–	H–C(3)	50.32	4.63
H–C(8')	132.67	7.56	2H–C(5)	48.90	3.61, 3.07
H–C(11)	132.19	7.52	2H–C(3')	43.57	4.26, 4.30
H–C(6')	128.30	8.37	2H–C(6)	42.94	4.40, 3.95
H–C(9)	127.86	8.28	2H–C(2')	(42.94)	3.81
H–C(7) or H–C(10)	122.59	7.20	2H–C(2)	34.50	2.46, 1.94
C(5'a) or C(8a)	122.30	–	H–C(1)	25.14	3.10
H–C(10) or H–C(7')	122.10	7.20	CH_3–C(1)	22.98	1.41

[a]) δ Values in ppm at 100.6 MHz (^{13}C) and 400.1 MHz (^{1}H) of a saturated solution (*ca.* 10 mg/ml) in $CDCl_3$ at 25°; internal standard TMS; in addition to the ^{1}H-NMR signals given, there is a br. *s* at 6.0 ppm for 1 NH.

signals for 2 sets of 4 aromatic protons, for 1 NH group, and for 2 NCH_2CH_2N fragments. Additional signals revealed the presence of the structural element $CHCH_2CHCH_3$. In the broad-band-decoupled 100.6-MHz ^{13}C-NMR spectrum, 25 *s* were observed, indicating one accidental overlap of 2 *s* at 42.94 ppm (see *Table 3* for chemical shifts and assignments). The relative configuration at C(1) and C(3) followed from H,H coupling constants and NOE difference experiments: the $^3J(2,3)$ were 11.5 and 2.5 Hz, indicating a quasi-axial disposition of H–C(3), and $^3J(1,2)$ were 5.5 and 1.5 Hz, compatible with a quasi-equatorial position of H–C(1). Irradiation of the CH_3–C(1) signal at 1.41 ppm led to an NOE enhancement for the signals of H–C(1), H–C(3), and the equatorial H–C(2). These results are best compatible with a sofa conformation **58** of the six-membered ring D, in which the CH_3 group adopts a quasi-axial position. The NOE experiments also allowed to differentiate between the signals for H–C(9') and H–C(12) at 7.42 and 7.31 ppm: irradiation of the CH_3 signal or the signal of H–C(1) resulted in a NOE at 7.31 ppm, thus allowing to assign this signal to H–C(12).

The MS of **53** showed the $M^{+\cdot}$ at *m/z* 424 in addition to prominent fragments at *m/z* 238, 223, 213, and 186. *Scheme 2* presents plausible fragmentation pathways.

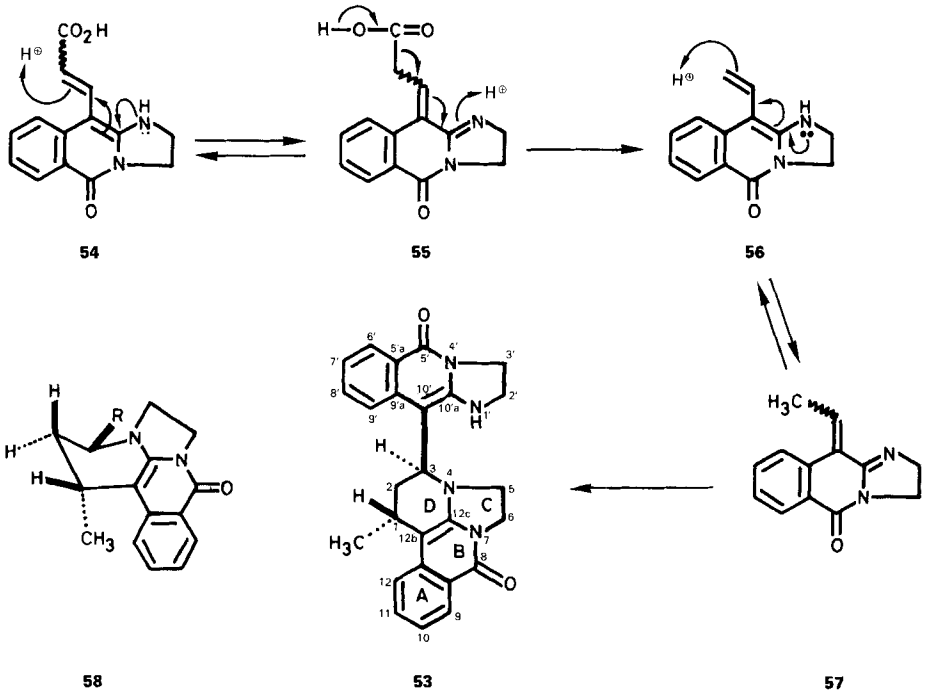
Scheme 2



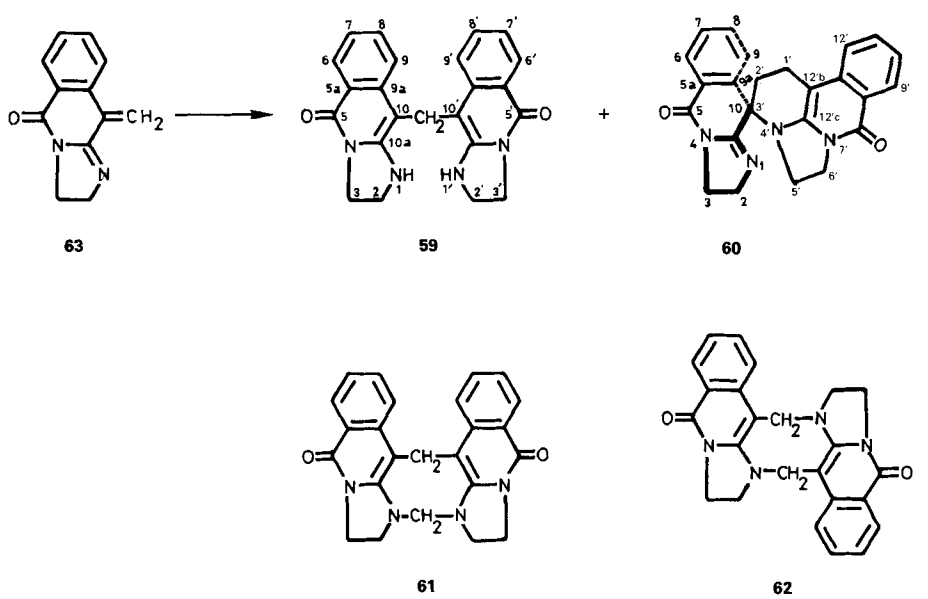
A plausible mechanism for the formation of **53** is shown in *Scheme 3*. We believe that the initial adduct **54** of **2** with propiolic acid tautomerises to **55** which decarboxylates to form the dienamine **56**, existing in equilibrium with the vinyl imine **57**. A 4+2 addition between **56** and **57**, with the vinyl group of the former as the dienophile and the azadiene system in the latter as diene would lead to the production of **53**. In accordance with this rationalization, we have noted that the reaction of **2** with acetaldehyde in dioxane produces **53**, although in low yield, presumably through the intermediacy of **57**.

3.2.5. *Reaction with Formaldehyde.* An equally interesting and unexpected reaction of **2** was the one with formaldehyde. In an attempt to run a *Mannich* reaction at C(10), **2** was treated with formalin and 2 mol-equiv. of morpholine at 70° for 2 h. Upon cooling, a product was obtained while evaporation of the filtrate gave another, each corresponding in weight to roughly 50% of the starting material. Incorporation of morpholine did not occur; both compounds could be obtained by using formaldehyde alone. Their high

Scheme 3



Scheme 4



m.p.'s suggested that they had incorporated two units of **2**, and their spectral analysis allowed the assignment of structure **59** to the former and **60** to the latter *(Scheme 4)*.

Compound **59** had analytical values corresponding to $C_{23}H_{20}N_4O_2$. The UV spectrum (MeOH) suggested the presence of *two* units per molecule of the chromophore present in **2**. The IR spectrum had bands at 3400, 3200, 1660, and 1600 cm^{-1}. The FD-MS showed $M^{+\cdot}$ at *m/z* 384 and a (low-abundance) doubly charged molecular ion M^{++} at *m/z* 192; at elevated emitter temperatures, major fragment ions at *m/z* 186 and 198 were also observed corresponding to complementary portions of the molecule *(Scheme 5)*. In the EI-MS, no $M^{+\cdot}$ but only *m/z* 186 and 198 appeared. The ^{1}H-NMR spectrum (400 MHz) and ^{13}C-NMR spectrum (100.6 MHz) in (D_6)DMSO confirmed the symmetry of the molecule. Detailed assignments are presented in *Table 4*.

Compound **60** had analytical values corresponding to $C_{24}H_{20}N_4O_2$. The UV spectrum showed the presence of only one unit of the chromophore in **2** in contrast to **59**. The IR spectrum had no bands for NH but showed absorption at 1660, 1630, 1610, and 1590 cm^{-1}. Only $M^{+\cdot}$ at *m/z* 396 and its doubly charged counterpart M^{++} at 198 appeared in the FD-MS. Indicating a higher stability towards fragmentation in comparison to **59**, the EI-MS of this spirocyclic, *i.e.* doubly bridged, dimer **60** also exhibited a pronounced $M^{+\cdot}$ at *m/z* 396 (composition confirmed by HR-MS). Major fragments were observed at *m/z* 210 ($C_{13}H_{10}N_2O$) and 186 ($C_{11}H_{10}N_2O$; *Scheme 5*). The former requires the presence of a C–C bond linking the 2 methylene groups introduced by CH_2O. The structural

Scheme 5

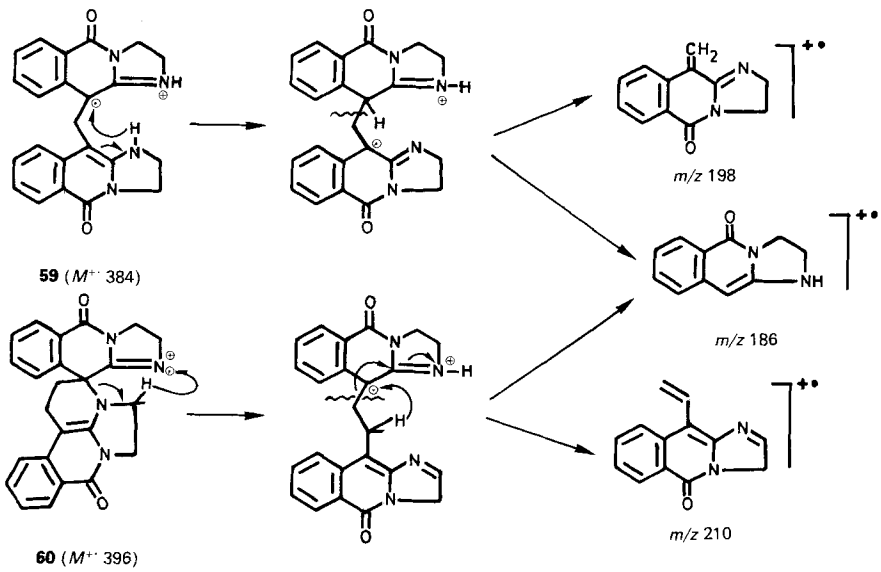


Table 4. *^{13}C- and ^{1}H-NMR Data for* **59**[a])

C/H	δ_C	δ_H	C/H	δ_C	δ_H
C(5, 5')	159.39	–	H–C(5a, 5a')	120.39	–
C(10a, 10a')	145.78	–	H–C(10, 10')	86.40	–
C(9a, 9a')	139.75	–	2H–C(3, 3')	44.24	4.15
H–C(8, 8')	131.74	7.38	2H–C(2, 2')	41.91	3.71
H–C(6, 6')	126.69	7.97	CH_2–C(10)	22.39	3.75
H–C(9, 9')	121.33	7.46	2NH	–	7.01
H–C(7, 7')	120.92	7.01			

[a]) δ Values in ppm at 100.6 (^{13}C) and 400.1 (^{1}H) MHz of a (D_6)DMSO solution (*ca.* 3 mg/ml) at 25°. Internal standard TMS.

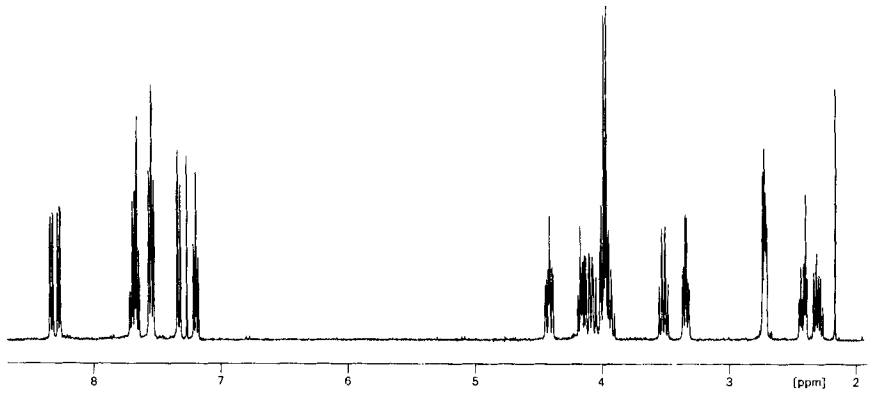


Fig. 2. *400-MHz ^{1}H-NMR spectrum of* **60** *in $CDCl_3$* (10 mg/ml). The *s* at 7.26 ($CHCl_3$) and 2.16 ppm stem from the solvent.

Table 5. *^{1}H- and ^{13}C-NMR Data for* **60**[a])

C/H	δ_C [ppm]	^1J(C,H) [Hz]	δ_H [ppm]	C/H	δ_C [ppm]	^1J(C,H) [Hz]	δ_H [ppm]
C(8′)	160.23	–	–	H–C(9)	125.38	161	7.66
C(5)	159.79	–	–	H–C(10′)	121.82	162	7.15
C(10a)	156.87	–	–	C(8′a)	121.45	–	–
C(12′c)	143.13	–	–	H–C(12′)	119.83	160	7.31
C(9a)	139.66	–	–	C(12′b)	85.30	–	–
C(12′a)	138.60	–	–	C(10)	58.63	–	–
H–C(8)	133.93	162	7.69	2H–C(2)	53.77	145	3.95
H–C(11′)	132.03	160	7.52	2H–C(3)	43.82	145	4.13, 3.95
H–C(7)	128.68	164	7.54	2H–C(5′)	43.77	145	3.50, 3.33
H–C(6)	128.43	166	8.26	2H–C(6′)	42.60	148	4.40, 4.07
H–C(9′)	127.73	162	8.30	2H–C(2′)	39.20	134	2.41, 2.29
H–C(5a)	126.40	–	–	2H–C(1′)	17.26	130	2.71

[a]) Saturated solution in $CDCl_3$.

alternatives **61** and **62** *(Scheme 4)* that would arise from a juncture of 2 molecules of **2** *via* two separate CH_2 bridges are, therefore, immediately ruled out.

The most compelling evidence in favour of structure **60** came from ^{1}H-, ^{13}C-, and ^{15}N-NMR studies at 400, 100.6, and 40.5 MHz, respectively. The ^{1}H-NMR spectrum (1% solution, $CDCl_3$; *Fig. 2* and *Table 5*) showed signals for 3 CH_2CH_2 fragments, 2 of which must belong to NCH_2CH_2N structural elements, as inferred from their chemical shifts. Since most of the CH_2 signals were anisochronous, the molecule must be chiral. Furthermore, signals for 8 aromatic protons were present, which could be partitioned into 2 sets of 4 contiguous protons (H–C(6) to H–C(9) and H–C(9′) to H–C(12′)) by selective decoupling experiments. An assignment to the 2 aromatic rings in **60** was achieved by NOE difference experiments: irradiation at 2.72 ppm (CH_2(1′)) led to a large NOE at 7.33 ppm (H–C(12′)). Irradiation at 2.41 ppm (1 H of CH_2(2′)) resulted in a somewhat smaller NOE at 7.65 ppm (H–C(9)).

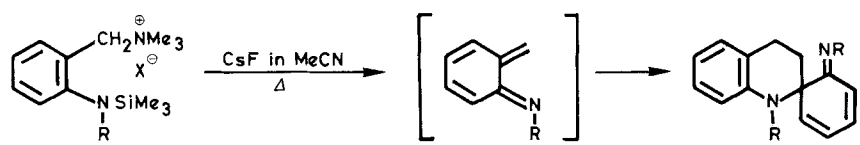
In the broad-band-decoupled 100.6-MHz ^{13}C-NMR spectrum (10% solution, $CDCl_3$), of **60** 24 separate *s* were observed. From chemical-shift considerations and with the help of undecoupled and selectively decoupled spectra with high (decoupling of one-bond couplings) and low (decoupling of long-range couplings) decoupler power, all signals except the ones for C(10a) and C(12′c) could be unambiguously assigned (see *Table 5*). The latter were differentiated with the help of ^1J(C,C) coupling constants, measured from satellite signals in a broad-band decoupled spectrum with a digital resolution of 0.2 Hz: the signal at 156.87 ppm with ^1J = 55.4 Hz (coupling between an sp^3- and sp^2-hybridised C-atom [12]) was attributed to C(10a) and the signal at 143.13 ppm with ^1J = 78.4 Hz (coupling between 2 sp^2-hybridised C-atoms across a double bond [12]) to C(12′c).

Finally, the broad-band decoupled 40.5-MHz ^{15}N-NMR spectrum (10% solution, $CDCl_3$) of **60** showed 4 signals, the two at 251.3 and 76.3 ppm (referenced to liq. NH_3 [13]) being assigned to N(1) and N(4'), respectively. A differentiation between the signals at 154.3 and 146.0 ppm was achieved with a selective decoupling at 3.95 ppm (3 H of CH_2(2) and CH_2(3)) with low power, resulting in appreciable decoupling at 154.3 ppm only, which, therefore, is assigned to N(4) (N(7') at 146.0 ppm).

Interestingly enough, the UV spectrum of **60** in 2N HCl was practically the same as in MeOH showing that the enamine chromophore was unaffected, protonation occurring probably solely on N(1). In contrast, the UV spectrum of **59** in 2N HCl showed transformation of the enamine chromophores to the ones of **2b**.

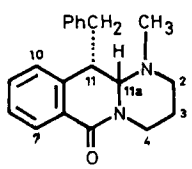
The formation of **59** and **60** from **2** evidently involves the intermediacy of **63**. A $[_4\pi_s+_2\pi_s]$ cycloaddition reaction of 2 molecules of **63**, one as an azadiene and the other as the dienophile (C=C) would lead to **60**. Heterodienophiles have enjoyed wide-spread synthetic utility, but few dienes incorporating heteroatoms in the conjugated system have been widely exploited, although interest in this topic is increasing [14] [15]. The formation of a spiro[cyclohexadiene-tetrahydroquinoline] **66** from **64** *via* **65** *(Scheme 6)* [16] [17] can be quoted as a precedent for our work, but it should be noted that our reactants and reagents are simpler. In contrast to the behaviour of such azadienes, it is reported that 2-vinylpyridine dimerises differently, although the HBr salt has been used [18].

Scheme 6

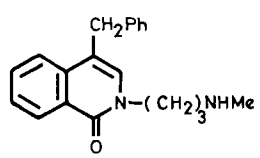


64 **65** **66**

3.2.6. *Some Reduction Reactions.* The 1(2*H*)-isoquinolinone **2** was unaffected by $NaBH_4$ and $LiAlH_4$; **38** was again resistant to $NaBH_4$; but **44** was reduced by $NaBH_4$ in MeOH solution to **67** (^{1}H-NMR: *d* (J = 4 Hz) for H–C(11a)). Assuming a *trans*-ring junction for the azaquinolizidine moiety and placing H–C(11a) in an axial conformation, the benzyl group at C(11) has to be located axially. Compounds **5** and **44** were unaffected by hot acid or alkali; **67** was resistant to the latter; hot acid, however, gave the ring-opened product **68** (^{1}H-NMR: 6.83 (*s*, H–C(3) and 3.98 ppm (*s*, PhCH_2)).



67



68

4. Conclusion. – The condensation of homophthalic acid (**1**) with various diamines gives rise to fused 1(2*H*)-isoquinolinones. They have enamine character and display a host of interesting reactions with synthetic potentials that await to be explored fully.

Experimental Part

1. *General.* M.p.: uncorrected. UV (λ_{max} in nm (log ε)) and IR spectra (cm^{-1}): *Beckman M 35* and *Perkin Elmer M 337* spectrophotometers (nujol mulls), resp. ^{1}H-NMR spectra: at 60 MHz on *Varian A60* and *EM 360* spectrometers, at 90 and 400 MHz on *Bruker WH 90* and *WM 400* spectrometers; δ_H rel. to TMS. ^{13}C-NMR

(100.6 MHz) and ^{15}N-NMR spectra (40.5 MHz): *Bruker WM 400* instrument; δ_C rel. to TMS as internal standard; δ_N measured with respect to external nitromethane and referenced to the 'liquid-ammonia scale' [13]. EI- and FD-MS: *Varian-MAT-CH5-DF* instrument equipped with a EI/FI/FD ion source. HR-MS: *CEC 21-110B* mass spectrometer using photoplate recording.

2. *Synthesis of Fused 2(1H)-Isoquinolinones* **2–6, 9–13, 23,** *and* **25.** A mixture of homophthalic acid (50 mmol) and diamine (100 mmol) was heated under reflux in *o*-dichlorobenzene (80 ml) for 6 h. The soln. was concentrated and diluted with hexane (200 ml). The precipitate was filtered off and crystallised. In the case of oily products, the crystalline salts were prepared. *2,3-Dihydroimidazo[1,2-b]isoquinolin-5(1H)-ones* **2**, **3**, **9**, and **10**, *1,2,3,4-tetrahydro-6H-pyrimido[1,2-b]isoquinolin-6-ones* **4–6**, **11**, and **12**, and *2,3,4,5-tetrahydro[1,3]diazepino[1,2-b]isoquinolin-7(1H)-one* (**13**) are listed in *Table 1*.

Homophthalic acid (= *2-carboxybenzeneacetic acid*; **1**) and *2-(aminomethyl)piperidine* (**22**) gave *1,2,3,4,4a,5-hexahydro-7H-pyrido[1',2':3,4]imidazo[1,2-b]isoquinolin-7-one* (**23**) in 14% yield. M.p. 160–161° (from MeOH). IR: 1600, 1630. ^{1}H-NMR ($CDCl_3$): 5.25 (*s*, H–C(12)); 8.20 (*m*, H–C(8)). Anal. calc. for $C_{15}H_{16}N_2O$ (240.32): C 74.97, H 6.71, N 11.66; found: C 74.54, H 7.00, N 11.60.

Similarly, *2-(2-aminoethyl)piperidine* (**24**) afforded *2,3,4,4a,5,6-hexahydro-1H,8H-pyrido[1',2':3,4]-pyrimido[1,2-b]isoquinolin-8-one* (**25**) in 85% yield. M.p. 140–142° (from EtOH). IR: 1640, 1620, 1600. ^{1}H-NMR ($CDCl_3$): 5.62 (*s*, H–C(13)); 8.28 (*m*, H–C(9)). Anal. calc. for $C_{16}H_{18}N_2O$ (254.32): C 75.56, H 7.13, N 11.02; found: C 75.85, H 7.40, N 10.90.

3. *Reactions of* **1** *with Other Amines.* With pentane-1,5-diamine, *2,2'-pentamethylenbis[isoquinoline-1,3(2H,4H)-dione]* (**14**) in 8% yield. M.p. 205–206° (from $CHCl_3$/EtOH). IR: 1720, 1680, 1600. Anal. calc. for $C_{23}H_{22}N_2O_4$ (390.42): C 70.75, H 5.68, N 7.18; found: C 70.30, H 5.97, N 6.95.

With 2-aminoethanol, *2-(2-hydroxyethyl)isoquinoline-1,3(2H,4H)-dione* (**18**) in 50% yield. M.p. 141–143°. Anal. calc. for $C_{11}H_{11}NO_3$ (205.22): C 64.38, H 5.40, N 6.83; found: C 64.63, H 5.53, N 6.93.

With 2-aminoethanthiol, *2-(2-mercaptoethyl)isoquinoline-1,3(2H,4H)-dione* (**19**) in 19% yield. M.p. 90–92°. Anal. calc. for $C_{11}H_{11}NO_2S$ (221.22): C 59.72, H 5.01, N 6.33; found: C 59.67, H 5.25, N 6.60.

With semicarbazide, *bi[isoquinoline]-1,1',3,3'(2H,2'H,4H,4'H)-tetrone* (**21**) in 32% yield. M.p. 308–310° (from DMF). IR: 1750, 1720, 1600. MS: 320 ($M^{+\cdot}$). Anal. calc. for $C_{18}H_{12}N_2O_4$ (320.30): C 67.50, H 3.78, N 8.75; found: C 67.65, H 4.20, N 9.13.

With 2-carboxy-4-nitrobenzeneacetic acid (**15**) and ethylenediamine, *4,5-dihydro-2-(2'-methyl-5'-nitrophenyl)-1H-imidazol* (**16**) in 25% yield. M.p. 132–134° (from $CHCl_3$/hexane). IR: 3280, 3200, 1630. MS: 205 ($M^{+\cdot}$). ^{1}H-NMR ($CDCl_3$): 2.55 (*s*, CH_3); 3.75 (*s*, CH_2CH_2); 4.90 (br. *s*, NH); 7.33 (*d*, H–C(3')); 8.05 (*dd*, H–C(4')); 8.25 (*d*, H–C(6')).

4. *Reaction of* **2** *with Acyl Chlorides and Sulfonyl Chlorides.* A soln. of **2** (5.6 g, 30 mmol), acyl or sulfonyl chloride (30 mmol), and Et_3N (3 g) was heated under reflux for ½ h and the solvent distilled off. The residue was triturated with H_2O and filtered. The product was crystallised from appropriate solvent; *1-acyl- and 1-sulfonyl-2,3-dihydroimidazo[1,2-b]isoquinolin-5(1H)-ones* **26–30** are listed in *Table 2*.

In the case of benzoyl chloride, the crude product (80%) from **2** (5 mmol) was chromatographed over 20 g of silica gel. Elution with CH_2Cl_2/EtOAc 1:1 gave in the earlier fractions *1-benzoyl-2,3-dihydroimidazo[1,2-b]isoquinolin-5(1H)-one* (**27**; 55%). HR-MS: 290.105 ($M^{+\cdot}$). The later fractions afforded the *10-benzoyl-2,3-dihydroimidazo[1,2-b]isoquinolin-5(1H)-one* (**35**; 15%). M.p. 207–211°. Yellow crystals (from CH_2Cl_2/Et_2O). IR: 3320, 1660, 1615. ^{1}H-NMR ((D_6) DMSO): 3.90 (*m*, CH_2); 4.30 (*m*, CH_2); 6.50–7.50 (*m*, 8 arom); 8.23 (*m*, H–C(6)); 8.55 (br. *s*, NH). HR-MS: 290.105 ($M^{+\cdot}$). Anal. calc. for $C_{18}H_{14}N_2O_2$ (290.105): C 74.47, H 4.86, N 9.65; found: C 74.72, H 5.04, N 9.32.

In the case of TsCl the crude product (40%) from **2** (5 mmol) was crystallised twice from CH_2Cl_2/MeOH/Et_2O to afford the yellow *10-tosyl-2,3-diydroimidazo[1,2-b]isoquinolin-5(1H)-one* (**36**; 10%). M.p. 270–273° (dec.). IR: 3380, 1660, 1600. ^{1}H-NMR ($CDCl_3$/(D_6)DMSO): 2.33 (*s*, CH_3); 3.85 (*m*, CH_2); 4.20 (*m*, CH_2); 7.0–8.2 (*m*, 8 arom. H); 7.50 (br. *s*, NH). HR-MS: 340.088 ($M^{+\cdot}$). Anal. calc. for $C_{18}H_{16}N_2O_3S$ (340.088): C 63.52, H 4.74, N 9.65; found: C 63.60, H 4.76, N 8.23.

The mother liquour was evaporated and the residue chromatographed over silica gel as above to afford *1-tosyl-2,3-dihydroimidazo[1,2-b]isoquinolin-5(1H)-one* (**30**; 25%) as colourless crystals. M.p. 195–198° (from CH_2Cl_2/Et_2O). HR-MS: 340.090 ($M^{+\cdot}$).

p-Nitrobenzenesulfonyl chloride and **2** gave *2,3-dihydro-10-[(4'-nitrophenyl)thio]imidazo[1,2-b]isoquinolin-5(1H)-one* (**45**; 10%), after chromatography over silica gel. M.p. 273–275° (dec.; from CH_2Cl_2/MeOH), blackening at *ca.* 258°. IR (KBr): 3450, 1660, 1615. ^{1}H-NMR ((D_6)DMSO): 3.67 (2 H–C(2)); 4.24 (2 H–C(3)); 7.14 (H–C(7)); 7.30 (H–C(2')); 7.47 (H–C(9)); 7.50 (H–C(8)); 7.69 (NH); 8.05 (H–C(6)); 8.08 (H–C(3')). ^{13}C-NMR ((D_6)DMSO): 41.70 (C(2)); 44.86 (C(3)); 70.63 (C(10)); 120.54 (C(5a)); 120.66 (C(9)); 121.93 (C(7)); 124.09

(C(3',5')); 125.12 (C(2',6')); 127.19 (C(6)); 133.10 (C(8)); 140.35 (C(9a)); 144.73 (C(4')); 148.56 (C(1')); 153.79 (C(10a)); 160.05 (C(5)). MS: 339 (M^{+}). Anal. calc. for $C_{17}H_{13}N_3O_3S$ (339.26): C 60.17, H 3.86, N 12.39; found: C 60.22, H 4.13, N 12.14.

5. *Reaction of* **2** *with Isocyanates and Isothiocyanate.* A soln. of **2** (20 mmol) and isocyanate (20 mmol) in THF (150 ml) was heated under reflux for 6 h. The solvent was evaporated, and the colourless product crystallised; the *1-carbamoyl-2,3-dihydroimidazo[1,2-b]isoquinolin-5(1H)-ones* **31**–**34** are presented in *Table 2.*

p-Chlorophenyl isocyanate and **3** afforded *10-[N-(4-chlorophenyl)carbamoyl]-2,3-dihydro-1-methylimidazo[1,2-b]isoquinolin-5(1H)-one* (**47**; 37%). M.p. 280–282° (from DMF). IR: 3220, 3160, 1660, 1630, 1600. ^{1}H-NMR ((D$_6$)DMSO): 2.87 (*s*, CH_3N); 3.30–3.70 (*m*, CH_2); 3.80–4.20 (*m*, CH_2); 6.90–7.85 (*m*, 7 arom. H); 8.0 (*m*, H–C(8)). Anal. calc. for $C_{19}H_{16}ClN_3O_2$ (353.81): C 64.50, H 4.56, N 11.88; found: C 64.71, H 4.69, N 12.13.

Phenyl isothiocyanate and **2** gave *2,3-dihydro-10-[N-(phenyl)thiocarbamoyl]imidazo[1,2-b]isoquinolin-5(1H)-one* (**46**; 42%). M.p. 221–222° (from aq. DMF). IR: 3200, 1640, 1610. ^{1}H-NMR ((D$_6$)DMSO): 3.55 (*m*, CH_2); 4.0 (*m*, CH_2); 6.7–8.1 (*m*, arom. H). Anal. calc. for $C_{18}H_{15}N_3OS$ (321.38): C 67.28, H 4.71, N 13.08; found: C 67.58, H 4.96, N 13.14.

6. *Reaction of* **2** *with Dicyanodiamide.* Dicyanodiamide (5 mmol) and **2** · HCl (5 mmol) were fused together at 180° for 1 ½ h. The melt was cooled and dissolved in H_2O and the soln. filtered. The filtrate was evaporated and the sticky residue crystallised from aq. EtOH to afford *10-[N^1-(diaminomethylidene)amidino]-2,3-dihydroimidazo[1,2-b]isoquinolin-5(1H)-one hydrochloride* (**37**). Yield 61%. M.p. > 300°. Anal. calc. for $C_{13}H_{15}ClN_6O$ (306.77): C 50.8, H 4.48, N 27.4; found: C 50.37, H 5.06, N 27.04.

7. *Alkylations of* **2** *and* **5**. A soln. of **2** (10 mmol) and benzyl bromide (10 mmol) in $CHCl_3$ (50 ml) containing anh. K_2CO_3 (10 mmol) was heated under reflux overnight. The mixture was filtered and the filtrate evaporated. The residue was crystallised from $CHCl_3$/EtOH to afford *10-benzyl-2,3-dihydroimidazo[1,2-b]isoquinolin-5(1H)-one* (**38**; 72%). M.p. 243–245°. UV (MeOH): 230 (4.45), 298 (infl., 4.19), 305 (4.23), 377 (3.63). UV (2N HCl): 234 (4.02), 240 (4.00), 267 (4.03). IR: 3260, 1660. ^{1}H-NMR ((D$_6$)DMSO): 3.57 (br. *s*, NH); 3.62 (*m*, CH_2); 3.83 (*s*, $PhCH_2$); 4.05 (*m*, CH_2); 6.70–7.50 (*m*, 8 arom. H); 7.97 (*m*, H–C(8)). MS: 276 (M^{+}). Anal. calc. for $C_{18}H_{16}N_2O$ (276.33): C 78.23, H 5.84, N 10.14; found: C 78.06, H 6.11, N 10.51.

Similarly, *10-allyl-2,3-dihydroimidazo[1,2-b]isoquinolin-5(1H)-one* (**39**; 25%) was obtained. M.p. 200–201° (from EtOH). IR: 3220, 1650, 1600. ^{1}H-NMR ($CDCl_3$): 3.30 (*m*, $CH_2CH{=}CH_2$); 3.68 (*m*, CH_2); 4.25 (*m*, CH_2); 4.75, 5.25 (*m*, $CH_2CH{=}CH_2$); 5.83 (*m*, $CH_2CH{=}CH_2$); 6.9–7.77 (*m*, 3 arom H); 8.30 (*m*, H–C(8)).

Benzyl bromide (10 mmol) and **5** (10 mmol) heated in $CHCl_3$ (50 ml) under reflux overnight, afforded *1,2,3,4-tetrahydro-1-methyl-11-benzyl-6H-pyrimido[1,2-b]isoquinolin-6-one hydrobromide* (**44** · HBr; 98%). M.p. 250–251° (from MeOH/Et_2O). IR: 1710, 1620. Anal. calc. for $C_{20}H_{21}BrN_2O$ (385.38): C 62.34, H 5.49, N 7.27; found: C 62.17, H 5.71, N 7.10.

Basification gave **44**. M.p. 140–141° (from aq. EtOH). ^{1}H-NMR ($CDCl_3$): 2.0 (*t*, CH_2(3)); 2.83 (*s*, CH_3N); 3.15 (*t*, CH_2(2)); 4.15 (*s*, $PhCH_2$); 4.16 (*t*, CH_2(4)); 7.0–7.4 (*m*, 3 arom. H); 7.13 (*s*, C_6H_5); 8.45 (*m*, H–C(8)).

Excess MeI and **5** afforded *2,3,4,11-tetrahydro-1,11-dimethyl-6-oxo-6H-pyrimido[1,2-b]isoquinolinium iodide* (**42**; 72%). M.p. 254–255° (from EtOH/Et_2O). IR: 1700, 1620, 1600. Anal. calc. for $C_{14}H_{17}IN_2O$ (356.27): C 47.20; H 4.81, N 7.86; found: C 47.03, H 5.06, N 7.58.

8. *Reaction of* **2** *with Acrylic Acid and Acrylonitrile.* A mixture of **2** (25 mmol) and acrylic acid (25 mmol) in EtOH (50 ml) was heated under reflux for ½ h. The precipitate was collected and crystallised from AcOH to give *5,6-dihydro-1H,8H-pyrido[3,2,1-lm](imidazo[1,2-b]isoquinoline)-3(2H),8-dione* (**51**; 85%). M.p. 286–288°. IR: 1700, 1650, 1610. ^{1}H-NMR (CF_3COOH): 3.22 (*m* 2 H–C(1), 2 H–C(2)); 4.2–5.0 (*m*, 2 H–C(5), 2 H–C(6)); 7.4–8.15 (*m*, 3 arom H); 8.52 (*m*, H–C(11)). Anal. calc. for $C_{14}H_{12}N_2O_2$ (240.26): C 70.0, H 5.0, N 11.66; found: C 70.07, H 5.10, N 11.91.

With acrylonitrile, *10-(2-cyanoethyl)-2,3-dihydroimidazo[1,2-b]isoquinolin-5-(1H)-one* (**52**) was obtained in 25% yield. M.p. 227–228° (dec.; from MeOH). Anal. calc. for $C_{14}H_{13}N_3O$ (239.27): C 70.27, H 5.48, N 17.56; found: C 70.43, H 5.85, N 17.16.

9. *Reaction of* **2** *and* **4** *with Maleic Acid.* Treatment of **2** (25 mmol) and maleic acid (25 mmol) yielded *2,3,5,6-tetrahydro-3,8-dioxo-1H,8H-pyrido[3,2,1-lm](imidazo[1,2-b]isoquinoline)-1-carboxylic acid* (**48**; 70%). M.p. > 320°. IR: 1710, 1700, 1680, 1610. ^{1}H-NMR ((D$_6$)DMSO): 2.75–3.10 (*m*, 2 H–C(2)); 3.80–4.70 (*m*, H–C(1), 2 H–C(5), 2 H–C(6)); 7.40 (*m*, H–C(12)); 7.50–7.80 (*m*, H–C(10), H–C(11)); 8.20 (*m*, H–C(9)). MS: 284 (M^{+}). Anal. calc. for $C_{15}H_{12}N_2O_4$ (284.27): C 63.38, H 4.26, N 9.86; found: C 63.07, H 4.54, N 9.63.

Maleic acid and **4** similarly afforded *2,3,6,7-tetrahydro-3,9-dioxo-1H,5H,9H-pyrido[3,2,1-mn](pyrimido[1,2-b]isoquinoline)-1-carboxylic acid* (**50**; 15%). M.p. 234–235° (from EtOH). IR: 1710, 1640, 1600. Anal. calc. for $C_{16}H_{14}N_2O_4$ (298.29): C 64.42, H 4.73, N 9.39; found: C 64.75, H 5.10, N 9.22.

10. *Reaction of* **2** *with Propiolic Acid.* Propiolic acid (28 mmol) and **2** (20 mmol) were heated together in EtOH (100 ml) under reflux for 10 h. The mixture was cooled and the precipitated yellow solid filtered off. Crystallisation

from DMF gave *2,3,5,6-tetrahydro-1α-methyl-3β-(1,2,3,5-tetrahydro-5-oxoimidazo[1,2-b]isoquinolin-10-yl)-1H,8H-benzo[c]imidazo[1,2,3-ij]naphthyridin-8-one* (**53**; 90%). M.p. 285–288° (dec.). UV (MeOH): 226 (4.66), 302 (4.51), 372 (3.97). IR: 3380, 1680, 1620. MS: 424 ($M^{+\cdot}$). Anal. calc. for $C_{26}H_{24}N_4O_2$ (424.49): C 73.56, H 5.70, N 13.20; found: C 73.04, H 5.74, N 12.97.

11. *Reaction of* **2** *with Formaldehyde.* A mixture of **2** (3.8 g), formalin (4 ml), and morpholine (3.6 g) was heated in dioxane (200 ml) at 70° for 2 h. After initial dissolution, a light yellow solid separated. After cooling, the precipitate was filtered off and crystallised from DMF to give 1.8 g of *10,10'-methylenebis[2,3-dihydroimidazo[1,2-b]isoquinolin-5(1H)-one]* (**59**). M.p. 302–306° (dec.). UV (MeOH): 230 (4.73), 298 (4.45), 303 (4.45), 380 (3.99). IR: 3400, 3200, 1660, 1600. MS: 384 ($M^{+\cdot}$). Anal. calc. for $C_{23}H_{20}N_4O_2$ (384.42): C 71.86, H 5.24, N 14.58; found: C 71.85, H 5.46, N 14.69.

The dioxane filtrate was evaporated and the residue triturated with Et_2O. The solid was crystallised from DMF to afford 2.0 g of *2',3,3',5',6',10-hexahydrospiro[imidazo[1,2-b]isoquinoline-10,3'-1'H,8'H-pyrido[3,2,1-lm][imidazo[1,2-b]isoquinoline]-5(2H),8'-dione* **60**. M.p. 294–296° (dec.), depressed by admixture with **59**. After crystallisation from $CHCl_3$, m.p. 273–275° (dec.). UV (MeOH): 230 (4.51), 298 (infl., 4.19), 306 (4.22), 380 (3.66). IR: 1660, 1630, 1610, 1590. HR-MS: 396.159 ($M^{+\cdot}$). Anal. calc. for $C_{24}H_{20}N_4O_2$ (396.159): C 72.71, H 5.08, N 14.13, O 8.07; found: C 72.30; H 5.10, N 13.70, O 8.40.

12. *Reduction of* **44** *with* $NaBH_4$. A soln. of **44** (5 g) in MeOH (50 ml) was treated with $NaBH_4$ (0.5 g) in small portions. After 1 h, H_2O (100 ml) was added and the product extracted with Et_2O (200 ml). Evaporation of the Et_2O layer and trituration with hexane gave a solid. This was crystallised from the same solvent to give 3.6 g of *1,2,3,4,11,11α-hexahydro-1-methyl-11-benzyl-6H-pyrimido[1,2-b]isoquinolin-6-one* (**67**). M.p. 115–116°. ^{1}H-NMR ($CDCl_3$): 1.5–2.4 (*m*, 2 H–C(3)); 2.30 (*s*, CH_3N); 2.30–3.50 (*m*, 2 H–C(3), H–C(11), $PhCH_2$); 4.0 (*d*, H–C(11a)); 4.30–4.70 (*m*, 2 H–C(4)); 6.60 (*m*, H–C(10)); 6.70–7.40 (*m*, 7 arom. H); 8.03 (*m*, H–C(7)). Anal. calc. for $C_{20}H_{22}N_2O$ (306.40): C 78.40, H 7.24, N 9.14; found: C 78.59, H 7.13, N 8.96.

13. *Ring Cleavage of* **67**. A soln. of 0.5 g of **67** in 10 ml of 2N HCl was heated at 100° for 4 h. The soln. was evaporated. The residue was crystallised from EtOH/Et_2O to give 0.25 g of *2-[3-(methylamino)propyl]isoquinolin-1(2H)-one hydrochloride* **68**·HCl. M.p. 150–151°. Anal. calc for $C_{20}H_{23}ClN_2O \cdot H_2O$ (360.86): C 66.56, H 6.98, N 7.76; found: C 66.56, H 7.05, N 8.20. Data of oily free base: ^{1}H-NMR ($CDCl_3$): 1.90 (*quint.*, $CH_2CH_2CH_2NH$); 2.33 (*s*, CH_3N); 2.57 (*t*, $CH_2CH_2CH_2NH$); 3.98 (*s*, $PhCH_2$); 4.00 (*t*, $CH_2CH_2CH_2NH$); 6.83 (*s*, H–C(3)); 7.20 (*s*, C_6H_5); 7.10–7.60 (*m*, 3 arom. H); 8.45 (*m*, H–C(8)). MS: 306 ($M^{+\cdot}$), 248 (major fragment, $M^{+\cdot} - CH_3NHCH_2CH_2$).

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