Chemistry and pharmacology of some benzo[1,2]cyclohepta[3,4,5-*d,e*]isoquinolines

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The chemistry of 1,2,3,7,8,12*b*-hexahydro-, 1,7,8,12*b*-tetrahydro-, and 7,8-dihydrobenzo[1,2]cyclohepta[3,4,5-*d,e*]isoquinolines has been investigated, leading to the synthesis of a wide variety of derivatives bearing substituents in the 2- and 3-position. Also, the reactions of 1,7,8,12*b*-tetrahydrobenzo[1,2]cyclohepta[3,4,5-*d,e*]isoquinoline with 1-buten-3-one, methyl mercaptoacetate, and 3-mercaptopropionic acid have yielded representatives of three novel pentacyclic systems; benzo[4,5]cyclohepta[1,2,3-*g,h*]benzo[*a*]quinolizine, benzo[1,2]cyclohepta[3,4,5-*d,e*]thiazolo[2,3-*a*]isoquinoline, and benzo[1,2]cyclohepta[3,4,5-*d,e*]-1,3-thiazino[2,3-*a*]isoquinoline. The central nervous system and cardiovascular pharmacology of the compounds have been investigated and the results are presented.

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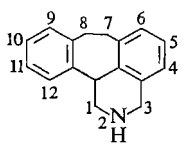
Synthetic routes to the benzo[1,2]cyclohepta-[3,4,5-*d,e*]isoquinoline ring system (e.g. **1**) have previously been developed by Humber *et al.* (1). This system contains the 5*H*-dibenzo[*a,d*]cycloheptene nucleus, which in turn is present in a number of clinically useful compounds (2) and we have therefore prepared a number of derivatives of **1** of diverse chemical types, for biological evaluation.

Chemistry

The compounds prepared are divided into 3 groups, the first consisting of 23 *N*-substituted derivatives of the 1,2,3,7,8,12*b*-hexahydro form of the ring system, **1**. The range of substituents introduced on nitrogen is shown in Table I where their physical and analytical data are collected. They were prepared from **1** by standard synthetic procedures as indicated in the Experimental section and in footnotes to Table I.



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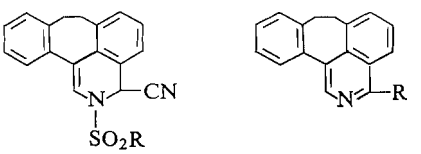
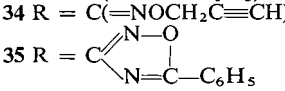
A second group of compounds comprises those bearing substituents at position-3 of the ring system. These were obtained by two routes, the first utilizing as starting material, 7,8-dihydrobenzo[1,2]cyclohepta[3,4,5-*d,e*]isoquinoline (**25**) (1) which was converted in good yield to the sulfonyl analogues of a Reissert compound, **26** and **27**, by the method recently described by Popp and co-workers (3), viz. the reaction with a benzene-sulfonyl chloride and potassium cyanide. They have shown that, in contrast to the behavior of classical Reissert compounds to sodium hydride which rearrange to give 1-benzoylisoquinolines (4) the "sulfonyl-Reissert compounds" yield isoquinoline-1-carbonitriles.



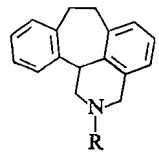
26 R = C_6H_5
27 R = 4-$CH_3C_6H_4$

25 R = H
28 R = CN
29 R = COOH
30 R = $CONH_2$
31 R = $C(=NOH)NH_2$
32 R = $C(=NOCOCH_3)NH_2$
33 R = $C(=NOCOC_6H_5)NH_2$
34 R = $C(=NOCH_2C{\equiv}CH)NH_2$
35 R = 

Thus, treatment of **27** with sodium hydride in xylene gave 86% of the carbonitrile **28** which was hydrolyzed to the carboxylic acid **29** with mineral acid. Alkaline hydrolysis of **28** gave the carboxamide **30**. The carbonitrile **28**, on reaction with hydroxylamine, was converted in high yield to the amidoxime **31** which, in turn, gave by acylation, the *O*-acetyl and *O*-benzoyl derivatives **32** and **33** respectively. The benzoylamidoxime **33**

TABLE I

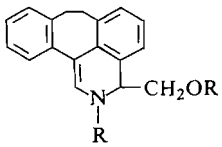
N-substituted 1,2,3,7,8,12*b*-hexahydrobenzo[1,2]cyclohepta[3,4,5-*d*,*e*]isoquinolines



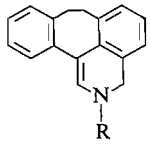
No.	R	Yield %	Melting point (°C)	Recrystallization solvent[1]	Formula	C % Calcd.	C % Found	H % Calcd.	H % Found	N % Calcd.	N % Found	Cl % Calcd.	Cl % Found
2	—CHO	67[2]	134–135	*a*	$C_{18}H_{17}NO$	82.10	82.10	6.51	6.26	5.32	5.39		
3	—$COCH_3$	92[3]	124–126	*a*	$C_{19}H_{19}NO$	82.29	81.72	6.91	6.71	5.05	5.14		
4	—$COOC_2H_5$	97[4]	98–100	*b*	$C_{20}H_{21}NO_2$	78.14	78.14	6.89	6.76	4.56	4.67		
5	—$COCHCl_2$	82[4]	132–133	*b*, *c*	$C_{19}H_{17}Cl_2NO$	65.90	65.79	4.95	5.05			20.48	20.72
6	—$COCH_2Cl$	84[4]	146–148	*d*	$C_{19}H_{18}ClNO$	73.20	72.90	5.82	5.88				
7	—$CO(CH_2)_2Cl$	86[4]	151–152	*c*, *d*	$C_{20}H_{20}ClNO$					4.30	3.96	10.88	10.94
8	—$COCH_2$(3,4-$[OCH_3]_2C_6H_3$)	76[4]	148–149	*c*	$C_{27}H_{27}NO_3$	78.42	78.52	6.58	6.40	3.39	3.37		
9	—$(CH_2)_2$(3,4-$[OCH_3]_2C_6H_3$)	68[5]	222–226	*d*, *e*	$C_{27}H_{29}NO_2 \cdot HCl$	74.38	74.22	6.94	6.95	3.21	3.02	8.13	8.31
10	—$COCH_2N(CH_3)_2$	62[6]	232–235[7]	*f*	$C_{21}H_{24}N_2O \cdot HCl$					7.85	7.51	9.93	9.70
11	—$CO(CH_2)_2N(CH_3)_2$	65[8]	90–91	*b*, *c*	$C_{22}H_{26}N_2O$					8.38	8.47		
12	—$CO(CH_2)_2NHCH_3$	68[9]	246–247	*e*, *g*	$C_{21}H_{24}N_2O \cdot HCl$					7.85	7.64		
13	—$CO(CH_2)_2N(CHO)CH_3$	55[10]	158–160	*b*, *c*	$C_{22}H_{24}N_2O_2$	75.83	75.60	6.94	6.92	8.04	7.99		
14	—$(CH_2)_2N(CH_3)_2$	58[11]	> 200	*a*, *f*	$C_{21}H_{26}N_2 \cdot 2HCl$					7.41	6.80	18.7	18.4
15	—$(CH_2)_3N(CH_3)_2$	84[12]	> 200	*e*, *g*	$C_{22}H_{28}N_2 \cdot 2HCl$					7.12	7.31	18.02	17.34
16	—NO	84[13]	140–141	*d*, *c*	$C_{17}H_{16}N_2O$	77.25	77.71	6.10	6.33				
17	—NH_2	45[13]	238–241	*g*	$C_{17}H_{18}N_2 \cdot HCl$					9.77	9.85	12.36	12.66
18	—$C(NH_2)$=NH	48[13]	> 200	*d*, *h*	$C_{18}H_{19}N_3 \cdot O \cdot 5H_2SO_4 \cdot O \cdot 5H_2O$[14]	64.50	64.28	6.31	6.42	12.53	12.16		
19	—CH_2CN	85[13]	119–121	*b*, *i*	$C_{19}H_{18}N_2$	83.17	82.92	6.61	6.52	10.21	10.25		
20	—CH_2CONH_2	70[13]	202–204	*d*	$C_{19}H_{20}N_2O$	78.05	78.52	6.90	7.16	9.58	9.60		
21	—$CONH_2$	75[13]	206–208	*d*, *e*	$C_{18}H_{18}N_2O$	77.67	77.31	6.52	6.69	10.07	9.85		
22	—SO_2NH_2	37[13]	220–222[15]	*d*	$C_{17}H_{18}N_2SO_2$	64.95	64.68	5.77	5.85	8.91	8.63		
23	—$CH_2C(NH_2)$=NOH	85[16]	187–189	*d*, *e*	$C_{19}H_{21}N_3O \cdot 2HCl$	60.01	59.80	6.10	6.25			18.65	18.34
24	—$CH_2C(NH_2)$=NOCOCH$_3$	88[17]	156–157	*j*	$C_{21}H_{23}N_3O_2$	72.18	72.02	6.63	6.43	12.03	12.10		

[1]*a*, acetone; *b*, hexane; *c*, benzene; *d*, ethanol; *e*, ether; *f*, 2-propanol; *g*, methanol; *h*, water; *i*, ethyl acetate; *j*, acetonitrile.
[2]From **1** and formic–acetic anhydride (11).
[3]By reaction of **1** with acetic anhydride in pyridine.
[4]By the reaction of **1** with the appropriate acyl chloride in ethylene dichloride and aqueous NaOH solution (e.g. see ref. 1).
[5]By reduction of **8** with $LiAlH_4$ in tetrahydrofuran.
[6]By heating **6** with an excess of dimethylamine in ethanol for 16 h in a sealed tube.
[7]The free base has m.p. 123–125° (benzene–hexane).
[8]By treating **7** as described in footnote 6.
[9]By treatment of **7** with methylamine as described in footnote 6.
[10]From **12** and formic–acetic anhydride (11).
[11]Reduction of **10** with $LiAlH_4$ in tetrahydrofuran.
[12]Reduction of **11** with $LiAlH_4$ in tetrahydrofuran.
[13]See Experimental section.
[14]Anal. Calcd.: S, 4.78; H_2O, 2.68. Found: S, 4.76; H_2O, 2.49.
[15]Anal. Calcd.: S, 10.18. Found: S, 10.07.
[16]By treatment of **19** with hydroxylamine (see preparation of **31** in Experimental section).
[17]By treatment of **23** with acetic anhydride in pyridine.

was converted to the 1,2,4-oxadiazole **35** by azeotropic removal of water from a refluxing xylene solution. The propargyl ether **34** was obtained from **31** and propargyl bromide. Reaction of the carboxylic acid **29** with lithium aluminium hydride resulted in reduction of the 2,3-double bond as well as the carboxyl group, yielding the 1,2-dihydroisoquinoline derivative **36** which was characterized as the *O*,*N*-diacetate **37**. Similar reduction of **25** gave the corresponding 1,2-dihydroisoquinoline **38** as a crystalline solid which decomposes on prolonged standing. It was characterized as the acetyl derivative **39**.

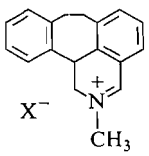


36 R = H
37 R = $COCH_3$

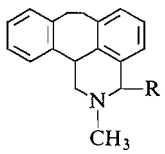


38 R = H
39 R = $COCH_3$

An alternative method of introducing substituents at the 3-position of the benzo[1,2]cyclohepta[3,4,5-*d*,*e*]isoquinoline system was available through reaction of the quaternary Schiff base methiodide **40***a* with 3-dimethylaminopropylmagnesium chloride to yield **41**, bearing a basic side chain at the desired site. Additionally, the pseudo-base **42** was obtained from **40***a* with sodium hydroxide, and reaction of **42** with cyanide ion gave the pseudonitrile **43**. Treatment of **42** with ethereal hydrogen chloride gave **40***b* as a hydrate.

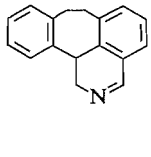


40*a* X = I
40*b* X = Cl



41 R = $(CH_2)_3N(CH_3)_2$
42 R = OH
43 R = CN

A third class of compounds, the novel pentacyclic systems **45**–**47**, was obtained by reaction of the Schiff base **44** (1) with various bifunctional reagents. Thus, the elegant benzoquinolizine synthesis using 1-buten-3-one (5) gave the benzo[4,5]cyclohepta[1,2,3-*g*,*h*] benzo[*a*] quinolizinone **45** as a mixture of 15*b*-α and 15*b*-β isomers (see structural formula) which were not isolated. Treatment of **44** with 2- or 3-mercapto acids or esters (6) gave the thiazolo- and thiazino-[2,3-*a*]isoquinolines **46** and **47** respectively and the latter was oxidized with *m*-chloroperbenzoic acid to the sulfoxide **48**.



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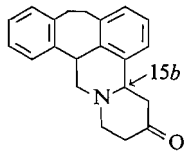

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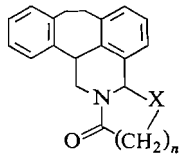
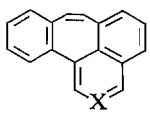
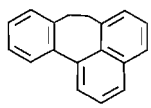


46 X = S, *n* = 1
47 X = S, *n* = 2
48 X = SO, *n* = 2

We have also been interested in obtaining the fully unsaturated form (**49**) of the benzo[1,2]cyclohepta[3,4,5-*d*,*e*]isoquinoline ring system and have indicated that this was not accessible by palladium dehydrogenation of the 1,7,8,12*b*-tetrahydro derivative **44**, which gives only the 7,8-dihydro form **25**, in high yield (1). A similar reluctance to form the fully unsaturated carbocyclic analogue **50** by attempted dehydrogenation of **51**, by a variety of methods, has recently been reported (7). We have thus attempted to obtain



49 X = N
50 X = CH



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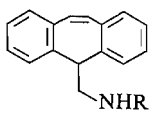

52 R = H
53 R = CHO
54 R = $COOC_2H_5$

the ring system with a 7,8-double bond by a Bischler–Napieralski reaction with the formamide **53**. Under a variety of experimental conditions (1) these attempts have not met with success, either with **53** or, with the related *N*-carbethoxy derivative **54**. The required amine (**52**)[1] for the preparation of the Bischler–Napieralski substrates was obtained by the lithium aluminium hydride – aluminium chloride reduction of 5*H*-dibenzo[*a*,*d*]cycloheptene-5-carbonitrile (9).

Pharmacology

The pharmacological properties of the compounds described in this study, as well as of some related compounds described previously, were determined. Effects on the central nervous system such as narcosis potentiation, protection against maximal electroshock seizures (MES), ataxic effect, as well as acute toxicity were studied in

[1]Compound **52** has recently been reported, without characterization, see ref. 8.

TABLE II

Effects of selected compounds on central nervous system parameters[1]

Compound	Acute toxicity LD_{50}:mg/kg	Narcosis potentiation ED_{50}:mg/kg	MES ED_{50}:mg/kg	Ataxia ED_{50}:mg/kg
55[2]	195	2.6	45	49
45	>1200	28	25.0	6.4
13	650	26	62	>160
44	260	18.6	40	36
3	475	25	72	60
56[3]	650	70	89	83
52	55	11	6.4	>10
57[4]	80	6.8	7	10.5
21	650	30	67	80
58[5]	700	27	54	120
59[6]	175	8	12.7	37
2	680	39	53	160
53	350	10	11	39
54	730	26.5	26	172
Amitriptyline HCl	94	9	11	40

[1]All compounds were injected intraperitoneally in albino mice.
[2]2-Methyl-1,2,3,7,8,12*b*-hexahydrobenzo[1,2]cyclohepta[3,4,5-*d*,*e*]isoquinoline hydrochloride. See ref. 1 for preparation.
[3]1,2,3,7,8,12*b*-Hexahydrobenzo[1,2]cyclohepta[3,4,5-*d*,*e*]isoquinolin-3-one. See ref. 1 for preparation.
[4]10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-methylamine. See ref. 1 for preparation.
[5]*N*-Carbethoxy 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-methylamine. See ref. 1 for preparation.
[6]*N*-Formyl 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene-5-methylamine. See ref. 1 for preparation.

mice by intraperitoneal administration (10). Virtually all of the compounds were investigated in the above tests and those which exhibited significant activity at 1/4 of the LD_{50} are collected in Table II. For comparative purposes the antidepressant drug amitriptyline (10) is also included.

Notably, significant activity is observed with tricyclic compounds **52, 53, 54, 57, 58, 59** containing the dibenzo[*a*,*d*]cycloheptene ring system of amitriptyline, with tetracyclic benzo[1,2]cyclohepta[3,4,5-*d*,*e*] isoquinolines (**2, 3, 13, 21, 44, 55, 56**) and, with the pentacyclic benzo[4,5]cyclohepta[1,2,3-*g*,*h*] benzo[*a*]quinolizine, **45**.

Several of the compounds of Table II were tested further in rats for their effects on conditioned avoidance and runway performance and on spontaneous motor activity (10). It was found in these tests that compound **55** has an activity profile similar to that of amitriptyline and the pharmacological activity and the possible therapeutic utility of this compound is under further study.

Several of the compounds were tested for their effects on blood pressure, respiration, intestinal tonus, and motility in urethane–chloralose anesthetized cats. The compounds were administered intravenously in increasing doses and those not having any effect at 20 mg/kg were considered to be inactive. The results with the other compounds are shown in Table III where the minimal doses required to cause a 20–30 mm Hg fall in blood pressure, are compared. With the exception of **1** the duration of the blood pressure fall produced by these compounds was short, the return to normal requiring less than 5 min. The magnitude of the blood pressure fall was dose-

TABLE III

Effects of selected compounds on blood pressure in cats[1]

Compound	Acute toxicity[2] LD_{50}(mg/kg)	Effect on blood pressure of cats: Dose (mg/kg) (intravenous)	Effect on blood pressure of cats: Blood pressure fall
1	120	0.5	+
8	>1200	20	0
9	>1200	20	0
10	190	0.5	+
14	140	0.5	+
15	160	0.5	+
17	125	3	+
18	—	20	0
25	325	0.5	+
31	175	20	0
40*b*	70	0.05	+
41	60	20	0
44	260	0.1	+
46	>1200	20	0

[1]Effect on blood pressure was studied by intravenous administration.
[2]LD_{50} determined intraperitoneally in the mouse.

dependent and the time course resembled that observed with parasympathomimetic agents. The most potent compound was **40***b*, the effect of which could be antagonized by atropine but not by hexamethonium. Further resemblance of **40***b* to parasympathomimetic agents was suggested by its stimulatory effect on the isolated guinea-pig ileum, an effect which was also antagonized by atropine.

The blood pressure fall caused by **1** was different from that of the other compounds, in that it was relatively long lasting; the duration of the decrease from a 1 mg/kg dose was more than 60 min.

Experimental

Melting points were taken on a Thomas–Hoover apparatus. Analyses were done by Mr. W. Turnbull and staff of our Laboratories.

*N-Nitroso-1,2,3,7,8,12b-hexahydrobenzo[1,2]cyclohepta-[3,4,5-d,e]isoquinoline (**16**)*

To a suspension of **1** (25 g) in 2-propanol (250 ml) and 2 *N* hydrochloric acid (200 ml) at 17° was added a solution of sodium nitrite (12.5 g) in water (60 ml). The mixture was heated to 75° for 3 h and another portion of sodium nitrite (12.5 g) was added and the solution kept at 75° for 12 h, diluted with water, and extracted with chloroform to yield 23.5 g of product, m.p. 140–141°.

*N-Amino-1,2,3,7,8,12b-hexahydrobenzo[1,2]cyclohepta-[3,4,5-d,e]isoquinoline (**17**)*

To a mixture of lithium aluminium hydride (1.38 g, 0.036 mole) in tetrahydrofuran (200 ml) was added **16** (9.5 g, 0.036 mole) dissolved in tetrahydrofuran. The mixture was stirred at room temperature for 3 h then worked up by conventional procedures to give the product as a gum which was converted to the hydrochloride salt.

*1,2,3,7,8,12b-Hexahydrobenzo[1,2]cyclohepta[3,4,5-d,e]-isoquinoline-2-carboxamidine Sulfate (**18**)*

A solution of *S*-methylpseudothiourea sulfate (7.24 g, 0.025 mole) in 1:1 ethanol:water (120 ml) was added over 5 min to **1** (11.9 g, 0.05 mole) in ethanol. The mixture was heated on the steam bath for 90 min. When the vigorous evolution of methyl mercaptan had subsided an additional portion of *S*-methylpseudothiourea sulfate (1.0 g) was added followed by heating for 4 h. On cooling a precipitate of **1**-sulfate was obtained. The ethanol was removed from the mother liquors *in vacuo*, the remaining aqueous solution treated with charcoal and diluted with acetone to give the product as a fluffy white solid.

*2-Cyanomethyl-1,2,3,7,8,12b-hexahydrobenzo[1,2]-cyclohepta[3,4,5-d,e]isoquinoline (**19**)*

To a solution of **1** (23.5 g, 0.1 mole) in absolute ethanol (100 ml) was added 70% aqueous glycolonitrile (16.4 g, 0.2 mole) followed by refluxing for 2 h. The cream-colored precipitate was collected and washed with cold ethanol.

*1,2,3,7,8,12b-Hexahydrobenzo[1,2]cyclohepta[3,4,5-d,e]-isoquinoline-2-acetamide (**20**)*

A mixture of **19** (5.0 g) and polyphosphoric acid (30 g) was stirred and heated at 120° for 3 h. Water was added, the mixture was made alkaline with sodium hydroxide, and extracted with chloroform to yield the product.

*1,2,3,7,8,12b-Hexahydrobenzo[1,2]cyclohepta[3,4,5-d,e]-isoquinoline-2-carboxamide (**21**)*

A refluxing solution of **1** (6.0 g) in benzene was treated with a slow stream of phosgene for 2 h. Hexane was added to obtain the *carbamoyl chloride* as a solid (5.7 g), m.p. 125–126° (petroleum ether, b.p. 80–120°). It was dissolved in liquid ammonia in a pressure bottle and allowed to stand at room temperature for 15 h. Evaporation of the ammonia gave the product as a solid.

*1,2,3,7,8,12b-Hexahydrobenzo[1,2]cyclohepta[3,4,5-d,e]-isoquinoline-2-sulfonamide (**22**)*

A solution of **1** (1.18 g, 0.005 mole) and sulfamide (0.5 g, 0.005 mole) was heated under reflux in 1,2-dimethoxyethane (20 ml) for 10 h. Evaporation of the solvent gave the product as a solid which was triturated with water, collected by filtration, and washed with hot benzene.

*2-Benzenesulfonyl-2,3,7,8-tetrahydrobenzo[1,2]-cyclohepta[3,4,5-d,e]isoquinoline-3-carbonitrile (**26**)*

Benzenesulfonyl chloride (14.66 g, 0.10 mole) was added over 2 h at 0° to a stirred mixture of **25** (11.55 g, 0.05 mole), potassium cyanide (9.75 g, 0.15 mole), water (20 ml), and methylenechloride (100 ml), and stirring was continued at 22° for 20 h. The reaction mixture was diluted with water and the organic phase washed (H_2O), dried (Na_2SO_4), treated with charcoal, and evaporated to yield the product as an amorphous solid (17.2 g, 86.5%). Two crystallizations from benzene–hexane gave analytically pure material, m.p. 186–188°.

Anal. Calcd. for $C_{24}H_{18}N_2O_2S$: C, 72.35; H, 4.55; N, 7.03; S, 8.03. Found: C, 72.46; H, 4.77; N, 6.66; S, 8.50.

By working in a similar manner but using *p*-toluenesulfonyl chloride instead of benzenesulfonyl chloride there was obtained (**27**) the *2-(p-toluenesulfonyl)* analogue of **26**, in 42% yield, m.p. 161–162° (2-propanol-methylenechloride).

Anal. Calcd. for $C_{25}H_{20}N_2O_2S$: C, 72.5; H, 4.86; S, 7.75. Found: C, 72.4; H, 4.71; S, 7.91.

*7,8-Dihydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinoline-3-carbonitrile (**28**)*

A mixture of **27** (16.9 g, 0.041 mole), xylene (75 ml), and sodium hydride (1.03 g, 0.043 mole; as a 50% suspension in mineral oil) was refluxed for 1 h. The cooled mixture was filtered, the solvent evaporated, and the residue passed through a column of alumina (20 g) in a benzene:chloroform (1:1) solution to yield the product as an oil which solidified on trituration with hexane, (8.6 g, 86%). The analytical sample had m.p. 134–135° (2-propanol).

Anal. Calcd. for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72; N, 10.93. Found: C, 84.14; H, 4.94; N, 10.51.

7,8-Dihydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinoline-3-carboxylic Acid (29)

Concentrated hydrochloric acid (10 ml) and carbonitrile **28** (1.00 g) were heated in a sealed tube at 150° for 16 h. On cooling the product was obtained as the *hydrochloride* salt, m.p. 184–186° (methanol) (1.1 g). The analytical sample had m.p. 184–186°.

Anal. Calcd. for $C_{18}H_{14}ClNO_2$: C, 69.10; H, 4.48; Cl, 11.34. Found: C, 69.10; H, 4.46; Cl, 11.23.

The free base was obtained by treating a suspension of the salt in methylene chloride with one equivalent of triethylamine. It had m.p. 154–155° (2-propanol).

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.05. Found: C, 78.20; H, 4.91; N, 4.76.

The acid was more conveniently prepared by refluxing the carbonitrile **28** with 48% hydrobromic acid to yield the hydrobromide salt, m.p. 208–213° (methanol), converted to the free base as above.

7,8-Dihydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinoline-3-carboxamide (30)

A solution of **28** (1.0 g) in 2-propanol (20 ml) containing potassium hydroxide (2.0 g) was refluxed for 3 h. Dilution with water, filtration, and thorough washing with water yielded the product (0.85 g), m.p. 193–194° (benzene–hexane).

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 79.09; H, 5.09; N, 10.06.

7,8-Dihydrobenzo[1,2]cyclohepta[3,4,5-d,e]isoquinolyl-3-amidoxime (31)

To a solution of hydroxylamine in methanol (prepared by treating hydroxylamine hydrochloride (2.24 g, 0.032 mole) in methanol with one equivalent of sodium methoxide and removing the sodium chloride by filtration) was added nitrile **28** (7.2 g, 0.028 mole) and the mixture was refluxed for 3 h. On cooling, the product (7.5 g, 92.5%) was obtained, m.p. 205–206°. The analytical sample had m.p. 210–211° (methanol). The *dihydrochloride* had m.p. 205–208° (methanol–ether).

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.53. Found: C, 74.69; H, 5.28; N, 14.58.

Anal. Calcd. for $C_{18}H_{17}Cl_2N_3O$: C, 59.69; H, 4.73. Found: C, 59.67; H, 5.02.

The *O-acetyl* derivative **32** was prepared with acetic anhydride in pyridine. It had m.p. 160–161° (benzene), ν_{max} ($CHCl_3$) 1758 cm^{-1}.

Anal. Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.59; H, 5.20; N, 12.57.

The *O-benzoyl* derivative **33** was prepared with benzoyl chloride in pyridine. It had m.p. 186–187° (benzene–hexane), ν_{max} ($CHCl_3$) 1738 cm^{-1}.

Anal. Calcd. for $C_{25}H_{19}N_3O_2$: C, 76.32; H, 4.87; N, 10.68. Found: C, 76.54; H, 4.98; N, 10.74.

The *propargyl ether* **34** was obtained in 83% yield by treating the amidoxime **31** in toluene with sodium hydride and propargyl bromide. It had m.p. 99–100° (benzene–hexane).

Anal. Calcd. for $C_{21}H_{17}N_3O$: C, 77.05; H, 5.24; N, 12.84. Found: C, 76.76; H, 5.18; N, 12.87.

3-(7,8-Dihydrobenzo[1,2]cyclohepta[3,4,5-d,e]-isoquinolyl)-5-phenyl-1,2,4-oxadiazole (35)

A xylene solution of **33** (0.5 g) was refluxed for 20 h in an apparatus with a Dean–Starke trap. On evaporation of the solvent the product was obtained as an oil. Filtration through a column of alumina in benzene:chloroform (1:1) solution gave a solid, m.p. 137–139° (440 mg). The analytical sample had m.p. 155–156° after three crystallizations from methanol.

Anal. Calcd. for $C_{25}H_{17}N_3O$: C, 79.88; H, 4.56; N, 11.19. Found: C, 79.82; H, 4.66; N, 11.23.

3-Acetoxymethyl-2-acetyl-2,3,7,8-tetrahydrobenzo[1,2]-cyclohepta[3,4,5-d,e]isoquinoline (37)

The acid **29** (1.32 g) was refluxed for 3 h in tetrahydrofuran (25 ml) with lithium aluminium hydride (1.52 g). A conventional workup gave 0.8 g of a solid, m.p. 155–163° (benzene) which was acetylated directly by heating for 10 min on the steam bath with acetic anhydride (0.5 ml) in pyridine (1.0 ml). Dilution with water and extraction with ether gave an amorphous solid which was filtered through a column of neutral alumina with benzene to yield the product (400 mg), m.p. 138.5–139° (methanol), λ_{max} (EtOH) 240 mμ (ε, 22 800); 308 mμ (ε, 12 700); ν_{max} ($CHCl_3$) 1735 cm^{-1} (O—Ac); 1670 cm^{-1} (N—Ac). The nuclear magnetic resonance (n.m.r.) spectrum showed one vinyl proton as a doublet centered at τ 3.41 and *N*- and *O*-acetyl methyl groups as singlets at τ 7.82 and 7.98 respectively.

Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.12; H, 6.01; N, 3.98.

2-Acetyl-2,3,7,8-tetrahydrobenzo[1,2]cyclohepta-[3,4,5-d,e]isoquinoline (39)

Compound **25** (5.6 g) was reduced with lithium aluminium hydride as described above to give the crude dihydroisoquinoline **38** as a solid (5.6 g), m.p. 111–114° on trituration with hexane, ν_{max} ($CHCl_3$) 3450 cm^{-1} (NH). It was acetylated as described above to yield the product, m.p. 173–175° (benzene–hexane), λ_{max} (EtOH) 240 mμ (ε = 23 100); 310 mμ (ε = 13 750); ν_{max} ($CHCl_3$) 1662 cm^{-1} (N—Ac); the n.m.r. showed one vinyl proton as a singlet at τ 3.32, and three acetyl methyl protons at τ 7.83 and the methylene protons adjacent to nitrogen as a singlet at τ 5.16.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.10; H, 6.11; N, 5.07.

2-Methyl-1,7,8,12b-tetrahydrobenzo[1,2]cyclohepta-[3,4,5-d,e]isoquinolinium Iodide (40a)

Compound **44** (20 g) was dissolved in acetone and refluxed for 2 h with methyl iodide (32 ml). Cooling and filtration gave bright yellow crystals of the product, m.p. 214–217° after crystallizing from ethanol, (23.5 g), ν_{max} KBr 1666 cm^{-1}; λ_{max} EtOH 290 mμ (ε = 14 250). Good iodine analyses could not be obtained with this compound.

Anal. Calcd. for $C_{18}H_{18}NI$: I, 33.83; N, 3.73. Found: I, 35.73; N, 3.72.

The corresponding *isoquinolinium chloride* (**40b**) was prepared from the pseudo base **42** with ethereal hydrogen chloride. It was crystallized from ethanol and was obtained as a hydrate, m.p. 155–160°, ν_{max} (KBr) 1666 cm^{-1}; λ_{max} (EtOH) 292 mμ (ε = 11 600).

Anal. Calcd. for $C_{18}H_{18}ClN \cdot H_2O$: C, 71.65; H, 6.60; N, 4.64. Found: C, 72.00; H, 6.68; N, 4.59.

2-Methyl-3-(3-dimethylaminopropyl)-1,2,3,7,8,12b-hexahydrobenzo[1,2]cyclohepta[3,4,5-d,e]-isoquinoline (41)

To a solution of 3-dimethylaminopropylmagnesium

chloride in tetrahydrofuran (120 ml) prepared from magnesium (0.72 g, 0.03 g-atom) and 3-dimethylaminopropyl chloride (3.6 g, 0.03 mole) was added compound **40***a* (7.4 g, 0.02 mole) portionwise with vigorous stirring. After the initial exothermic reaction had subsided, the mixture was refluxed for 3 h, cooled, and treated with 10% aqueous ammonium chloride (20 ml). The organic phase yielded the title compound as a gum (6.0 g). The dihydrochloride salt was prepared and crystallized from a methanol–acetone mixture. It had m.p. 207–210°.

Anal. Calcd. for $C_{23}H_{32}Cl_2N_2$: N, 6.88; Cl, 17.40. Found: N, 6.10; Cl, 17.35.

*3-Cyano-2-methyl-1,2,3,7,8,12b-hexahydrobenzo[1,2]-cyclohepta[3,4,5-d,e]isoquinoline (**43**)*

Compound **40***a* (9.8 g), dissolved in 50 ml of ethanol: water (1:1), was treated dropwise with sodium hydroxide (4.18 g) in water (7 ml) over 5 min at 0°. The mixture was stirred at 22° for 1 h, extracted with ether, and the ether phase washed with water and extracted with 1 *N* hydrochloric acid. The acid solution was treated with charcoal, made alkaline with 1 *N* sodium hydroxide, and the precipitated pseudobase **42** was washed with water and dried in a desiccator over KOH pellets. It weighed 6.6 g and had m.p. 113–118°, ν_{max} ($CHCl_3$) 3600 cm^{-1}. The pseudo-base **42** (1.32 g, 0.005 mole) was dissolved in methanol (25 ml) and treated dropwise with potassium cyanide (325 mg, 0.005 mole) in water (3.0 ml). The mixture was heated on the steam bath for 10 min, cooled, and the precipitate filtered. It was recrystallized from methanol to give the product (0.85 g), m.p. 157–158°.

Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 82.96; H, 6.46; N, 9.94.

*2-Oxo-1,2,3,4,6,6a,11,12-octahydro-15b H-benzo[4,5]-cyclohepta[1,2,3-g,h]benzo[a]quinolizine (**45**)*

Freshly distilled 1-buten-3-one (83 ml) was added to a solution of **44**·hydrochloride (28.0 g) in absolute ethanol (300 ml) at 15°. The mixture was refluxed for 6 h and concentrated to yield 32.0 g of solid which was dissolved in 5% ethanol in water (500 ml), made alkaline with sodium carbonate, and extracted to give an oil (26.6 g). Crystallization from acetonitrile gave the product (17.8 g), m.p. 162–164°. Thin-layer chromatography on anhydrous silica gel plates with 20% methanol in benzene revealed the presence of two spots which virtually touched each other, probably 15*b*-α and 15*b*-β isomers. The presence of isomers could not be detected if the plates were not absolutely dry.

Anal. Calcd. for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.08; H, 7.22; N, 4.41.

*1-Oxo-1,2,7,8,12,13-hexahydro-3aH-benzo[1,2]-cyclohepta[3,4,5-d,e]thiazolo[2,3-a]isoquinoline (**46**)*

A solution of compound **44** (23.35 g, 0.1 mole) and methyl mercaptoacetate (15.9 g, 0.15 mole) in xylene (250 ml) was refluxed for 24 h. On cooling the product (15.2 g) separated. On crystallization from acetone it had m.p. 205–206°.

Anal. Calcd. for $C_{19}H_{17}NOS$: C, 74.23; H, 5.58; N, 4.56; S, 10.43. Found: C, 74.29; H, 5.73; N, 4.41; S, 10.78.

The reaction of **44** with 3-mercaptopropionic acid as described above gave *1-oxo-2,3,8,9,13b,14-hexahydro-1H-benzo[1,2]cyclohepta[3,4,5-d,e]-1,3-thiazino[2,3-a]-isoquinoline* (**47**), m.p. 201–203° (chloroform–benzene).

Anal. Calcd. for $C_{20}H_{19}NOS$: C, 74.71; H, 5.96; N, 4.36; S, 9.99. Found: C, 74.39; H, 5.85; N, 4.34; S, 10.09.

*1-Oxo-2,3,8,9,13b,14-hexahydro-1H-benzo[1,2]cyclohepta[3,4,5-d,e]-1,3-thiazino[2,3-a]isoquinoline-S-oxide (**48**)*

A solution of 85% *m*-chloroperbenzoic acid (1.07 g, 0.005 mole) in methylene chloride (20 ml) was added dropwise to a solution of **47** (1.6 g, 0.005 mole) in methylene chloride (40 ml) at such a rate that the internal temperature did not exceed 35°. The solution was washed with aqueous sodium bicarbonate and the residue from the organic phase was chromatographed on alumina (neutral, activity II). Elution with 10–25% chloroform in benzene gave the product (0.55 g), m.p. 155° (benzene–hexane).

Anal. Calcd. for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68; N, 4.15. Found: C, 71.44; H, 5.81; N, 3.91.

*5H-Dibenzo[a,d]cycloheptene-5-methylamine (**52**) (8)*

5H-Dibenzo[*a*,*d*]cycloheptene-5-carbonitrile (9) (10.8 g, 0.05 mole), in a mixture of ether (100 ml) and tetrahydrofuran (30 ml), was added dropwise to a mixture of aluminium chloride (7.33 g, 0.05 mole) and lithium aluminium hydride (2.09 g, 0.05 mole) in ether (100 ml). The mixture was refluxed 3 h and water (9.0 ml) added. Filtration gave a precipitate which was distributed between chloroform and aqueous sodium hydroxide. The organic phase gave the product (6.1 g), m.p. 97–97.5° (hexane). The *hydrochloride* had m.p. >300° (methanol–ether). The *N-formyl* derivative **53** was prepared with formic–acetic anhydride (11) and had m.p. 118–119° (acetone).

Anal. Calcd. for $C_{16}H_{16}ClN$: C, 74.53; H, 6.26; Cl, 13.75. Found: C, 74.39; H, 6.25; Cl, 13.74.

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.03; N, 5.62. Found: C, 81.94; H, 6.09; N, 5.84.

The *N-carbethoxy* derivative **54** was obtained with ethyl chloroformate in ethylene dichloride and aqueous sodium hydroxide solution (1). It had m.p. 97–99° (ethanol).

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.41; H, 6.30; N, 4.64.

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