N-Alkylaminoalkyl Derivatives of Some Hexahydrobenzazocines

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The synthesis of several 3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-ones (III) by Beckmann rearrangement of the oximes of the corresponding 1,2-benzocyclohept-1-en-3-ones (II) is described. The lactams (III) were treated with sodamide and an alkylaminoalkyl chloride in dry xylene at reflux to give 1-alkylaminoalkyl-3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-ones (IV) which, on reduction with lithium aluminium hydride, afforded the corresponding 1-alkylaminoalkyl-1,2,3,4,5,6-hexahydrobenz[*b*]azocines (V) in good yield. Several transformations in the 1,2,3,4,5,6-hexahydrobenz[*b*]azocine series are described. Some 2-alkylaminoalkyl derivatives (XIII) of the isomeric 1,2,3,4,5,6-hexahydrobenz[*c*]azocine, the 3-(3-dimethylaminopropyl)derivative (X) of the isomeric 1,2,3,4,5,6-hexahydrobenz[*d*]azocine, and 3-(3-dimethylaminopropyl)-1,2-benzocyclo-oct-1-ene (XVII) were also prepared.

WHILE the psychopharmalogical activity of *N*-alkylaminoalkyl derivatives of some heterocyclic, tricyclic systems [1] has long been recognised, the corresponding derivatives of nitrogen-containing bicyclic systems have received less attention. Accordingly, we have investigated the synthesis of some hexahydrobenzazocines and related compounds.

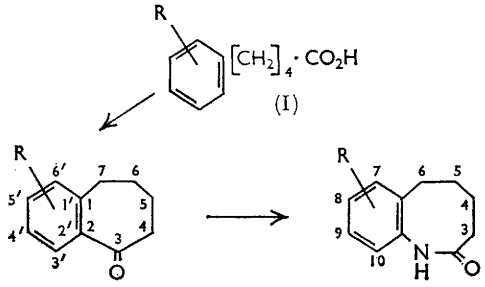
The 3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-ones (III) were obtained in good yields by Beckmann rearrangement of the oximes of the corresponding 1,2-benzocyclohept-1-en-3-ones (II) with concentrated sulphuric acid–glacial acetic acid (2 : 1).

For convenience, the unsubstituted lactam (IIIa) was prepared in excellent yield by Beckmann rearrangement of the oxime of 1,2-benzocyclohept-1-en-3-one (IIa) rather than by the reported Schmidt reaction on the ketone.[2]

Beckmann rearrangement of the oxime of 6′-chloro-1,2-benzocyclohept-1-en-3-one [3] (IIb) gave 7-chloro-3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-one (IIIb). Cyclisation of 5-(*m*-chlorophenyl)valeric acid (I; R = *m*-Cl) was shown to give 5′-chloro-1,2-benzocyclohept-1-en-3-one (IIc) since oxidation of the product afforded 4-chloro- rather than 3-chloro-phthalic acid. The Beckmann rearrangement of the corresponding oxime gave 8-chloro-3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-one (IIIc). The Sandmeyer reaction on 4′-amino-1,2-benzocyclohept-1-en-3-one [4] (IIe) gave the corresponding 4′-chloro-compound (IIf); Beckmann rearrangement of the oxime afforded 9-chloro-3,4,5,6-tetrahydrobenz-

[1] M. Gordon, 'Psychopharmacological Agents,' Medicinal Chemistry, vol. 4/I, Academic Press, New York, 1964.
[2] N. S. Hjelte and T. Agback, *Acta Chem. Scand.*, 1964, **18**, 191.
[3] R. Granger, H. Orzalési, and A. Muratelle, *Compt. rend.*, 1961, **252**, 1478.
[4] P. A. S. Smith and W. L. Berry, *J. Org. Chem.*, 1961, **26**, 27.

[*b*]azocine-2(1*H*)-one (IIIg). The 8-bromo-lactam (IIId) was prepared as described previously.[5]



(II) (III)

a; R = H
b; R = 6′-Cl
c; R = 5′-Cl
d; R = 4′-NO_2
e; R = 4′-NH_2
f; R = 4′-Cl

a; R = H
b; R = 7-Cl
c; R = 8-Cl
d; R = 8-Br
e; R = 9-NO_2
f; R = 9-NH_2
g; R = 9-Cl
h, R = 9(?)-SO_2NMe_2

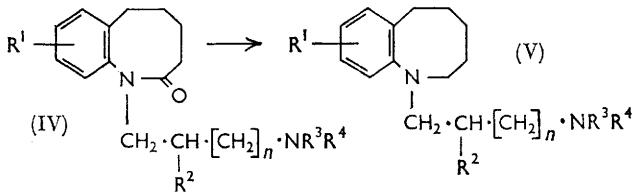
The only products that could be isolated from the Beckmann rearrangement investigated in this series were the benz[*b*]azocin-2-ones (III) formed as a result of phenyl rather than alkyl migration. This was proved by hydrolysis of the lactam with concentrated hydrochloric acid and coupling the diazotised product with β-naphthol to give bright orange-red dyes.

Nitration of 3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-one (IIIa) or nitration of 1,2-benzocyclohept-1-en-3-one (IIa) to give the 4′-nitro-derivative [4] (IId) followed by a Schmidt reaction afforded 9-nitro-3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-one (IIIe). The orientation of the nitro-group was proved unequivocally by degradation of the 9-nitro-lactam (IIIe) to the known 5-(*p*-nitrophenyl)valeric acid [6] (I; R = *p*-NO_2) by hydrolysis followed by reductive deamination. These observations are in direct contrast with those of Smith and Berry [4] on the nitration of the corresponding 4,5-dihydrobenz[*b*]azepin-2(3*H*)-one or nitration of α-tetralone followed by a Schmidt reaction where identical lactams were not obtained.

Catalytic hydrogenation of 9-nitro-3,4,5,6-hexahydrobenz[*b*]azocin-2(1*H*)-one (IIIe) afforded the 9-amino-lactam (IIIf); a Sandmeyer reaction on the amine (IIIf) gave the corresponding 9-chloro-lactam (IIIg).

The lactams (III) with sodamide in dry xylene at reflux point formed insoluble sodio-derivatives which were treated with the appropriate alkylaminoalkyl chloride to give (IV, a—i); reduction with lithium aluminium hydride afforded the required 1,2,3,4,5,6-hexahydrobenz[*b*]azocines (V, a—i).

Reaction of 1-(3-dimethylamino)-1,2,3,4,5,6-hexahydrobenz[*b*]azocine (Va) with ethyl chloroformate in benzene at reflux point gave the ethoxycarbonyl compound (Vj). This was heated under reflux with potassium hydroxide in carbitol [7] to give 1-(3-methylaminopropyl)-1,2,3,4,5,6-hexahydrobenz[*b*]azocine (Vk). Nitration of (Va) gave a mononitro-compound (Vl) which could be reduced catalytically to the corresponding amino-compound (Vm). A Sandmeyer reaction on



(IV) (V)

a *; *n* = 1, R^1 = R^2 = H, R^3 = R^4 = Me
b; *n* = 0, R^1 = R^2 = H, R^3 = R^4 = Et
c *; *n* = 1, R^1 = H, R^2 = R^3 = R^4 = Me
d; *n* = 1, R^1 = R^2 = H, R^3 = Me, R^4 = $CH_2C \equiv CH$
e; *n* = 1, R^1 = R^2 = H, NR^3R^4 = $-N{\cdot}CH_2{\cdot}CH_2{\cdot}NMe{\cdot}CH_2{\cdot}CH_2-$
f; *n* = 1, R^1 = 7-Cl, R^2 = H, R^3 = R^4 = Me
g; *n* = 1, R^1 = 8-Cl, R^2 = H, R^3 = R^4 = Me
h; *n* = 1, R^1 = 9-Cl, R^2 = H, R^3 = R^4 = Me
i; *n* = 1, R^1 = 8-Br, R^2 = H, R^3 = R^4 = Me
j; *n* = 1, R^1 = R^2 = H, R^3 = Me, R^4 = CO_2Et
k *; *n* = 1, R^1 = R^2 = R^3 = H, R^4 = Me
l; *n* = 1, R^1 = 9-NO_2, R^2 = H, R^3 = R^4 = Me
m; *n* = 1, R^1 = 9-NH_2, R^2 = H, R^3 = R^4 = Me
n; *n* = 1, R^1 = 9-NHAc, R^2 = H, R^3 = R^4 = Me
o; *n* = 1, R^1 = 9-NHEt, R^2 = H, R^3 = R^4 = Me
p; *n* = 1, R^1 = 9(?)-SO_2NMe_2, R^2 = H, R^3 = R^4 = Me

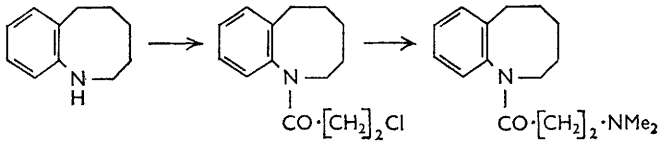
* Belg.P. 671,973/1966.

the amine (Vm) gave a chloro-compound (Vh) with a g.l.c. retention time and i.r. spectrum identical with those of the product obtained by the reaction of 9-chloro-3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-one (IIIg) with 3-dimethylaminopropyl chloride and reduction of the product with lithium aluminium hydride. It was different from the isomeric compounds (Vf) and (Vg).

Acetylation of 9-amino-1-(3-dimethylaminopropyl)-1,2,3,4,5,6-hexahydrobenz[*b*]azocine (Vm) afforded the acetyl derivative (Vn) which was reduced with lithium aluminium hydride to the 9-ethylamino-compound (Vo).

Chlorosulphonation of (Va) followed by treatment of the crude sulphonyl chloride with aqueous methylamine solution gave a dimethylsulphamoyl derivative (Vp). The orientation of the dimethylsulphamoyl group, most probably at position 9, was not established. In a similar manner, 3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-one (IIIa) gave a dimethylsulphamoyl derivative (IIIh).

The reaction of 1,2,3,4,5,6-hexahydrobenz[*b*]azocine [8]



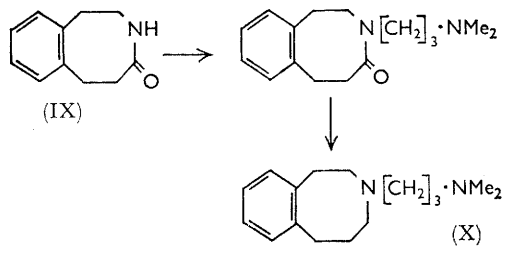
(VI) (VII) (VIII)

(VI) with β-chloropropionyl chloride followed by dimethylamination of the resulting chloride (VII) afforded a moderate yield of the amide (VIII).

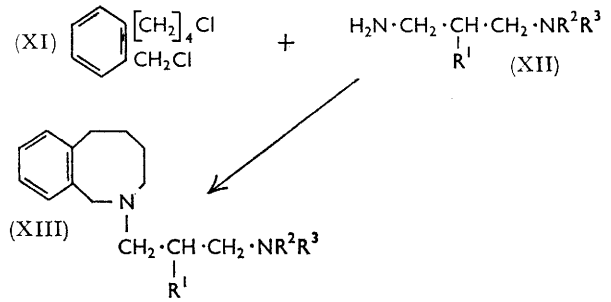
[5] R. Huisgen, I. Ugi, and H. Brade, *Annalen*, 1954, **586**, 30.
[6] L. D. Freedman and G. O. Doak, *J. Amer. Chem. Soc.*, 1949, **71**, 779.
[7] Belg.P. 620,541/1963.
[8] R. König and R. Huisgen, *Chem. Ber.*, 1959, **92**, 429.

Attempts to prepare any 10-substituted-1,2,3,4,5,6-hexahydrobenz[*b*]azocines were unsuccessful.

The *N*-3-dimethylaminopropyl derivative (X) of the isomeric benz[*d*]azocine was prepared in the usual manner *via* the sodio-derivative of 1,2,5,6-tetrahydrobenz[*d*]azocine-4(3*H*)-one [2] (IX).

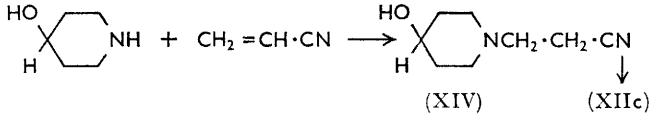


Some 1,2,3,4,5,6-hexahydrobenz[*c*]azocines (XIII) were prepared by the condensation of 4-(*o*-chloromethylphenyl)butyl chloride [9] (XI) with the appropriate amine (XII) in n-butanol at reflux point in the presence of lithium bromide and sodium carbonate.

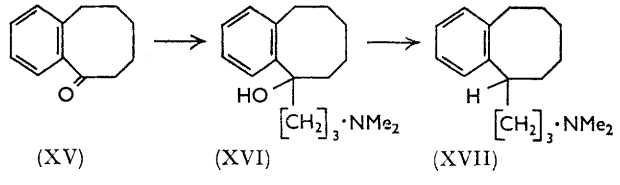


a; $R^1 = H$, $R^2 = R^3 = Me$
b; $R^1 = R^2 = R^3 = Me$
c; $R^1 = H$, NR^2R^3 = N·CH2·CH2·CH(OH)·CH2·CH2

The synthesis of the hitherto undescribed amine (XIIc) was achieved by the reaction of 4-hydroxypiperidine with acrylonitrile and catalytic hydrogenation of the product (XIV) in ethanolic ammonia.



The (XVII) was prepared in low yield by reaction of 3-dimethylaminopropyl magnesium chloride with 1,2-benzocyclo-oct-1-en-3-one [10] (XV) to give the



tertiary alcohol (XVI). This was dehydrated with acetic anhydride–sodium acetate to give a 1 : 2 : 5 mixture, as indicated by g.l.c., of isomeric olefins which was catalytically hydrogenated over palladium–charcoal to give the desired compound (XVII).

TABLE 1

N-Alkylaminoalkyl-3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-ones (IV)

No.	B.p./mm.	Yield (%)	Molecular formula	Calc. (%) C	H	N	Found (%) C	H	N
(IVa)	122—124°/0·07	62	$C_{16}H_{24}N_2O$	73·8	9·3	10·8	73·7	9·3	11·0
(IVb)	137—142/0·15	77·5	$C_{17}H_{26}N_2O$	74·4	9·6	10·2	74·1	9·6	10·2
(IVc)	130—134/0·1	80	$C_{17}H_{26}N_2O$	74·4	9·6	10·2	74·1	9·6	10·2
(IVd)	168—172/0·25	65	$C_{18}H_{24}N_2O$	75·5	8·5	9·8	75·8	8·4	9·6
(IVe)	176—180/0·05	82·5	$C_{19}H_{28}N_2O$	72·3	9·3	13·3	71·4	9·4	13·4

TABLE 2

N-Alkylaminoalkyl-1,2,3,4,5,6-hexahydrobenz[*b*]-azocines (V)

No.	B.p./mm.	Yield (%)	Molecular formula	Calc. (%) C	H	N	Found (%) C	H	N
(Va)	116—118°/0·2	91	$C_{16}H_{26}N_2$	78·0	10·6	11·4	77·8	10·5	11·7
(Vb)	104—105/0·2	86	$C_{17}H_{28}N_2$	78·4	10·8	10·8	78·1	10·7	10·8
(Vc)	98—100/0·3	80	$C_{17}H_{28}N_2$	78·4	10·8	10·8	78·1	10·5	10·4
(Vd)	122—124/0·1	44	$C_{18}H_{26}N_2$	79·9	9·7	10·4	78·6	10·0	10·8
(Ve)	160—166/0·1	77	$C_{19}H_{31}N_3$	75·7	10·4	13·9	76·0	10·3	13·8
(Vf)	158—162/0·3	58	$C_{16}H_{25}ClN_2$	68·4	9·0	10·0	68·4	9·2	10·0
(Vg)	114—120/0·1	77	$C_{16}H_{25}ClN_2$ †			10·0			9·9
(Vh)	120—123/0·1	90	$C_{16}H_{25}ClN_2$ ‡			10·0			9·8
(Vi)	144—146/0·2	40	$C_{16}H_{25}BrN_2$ §			8·6			8·4
(Vj)	146—153/0·3	48	$C_{18}H_{28}N_2O_2$	71·0	9·3	9·2	71·0	9·3	9·2
(Vk)	100/0·4	69	$C_{15}H_{24}N_2$	77·5	10·4	12·1	76·8	10·4	12·0
(Vl)	144—149/0·5	92	$C_{16}H_{28}N_2O_2$	66·0	8·7	14·4	66·2	8·5	14·1
(Vm)	138—142/0·1	78	$C_{16}H_{27}N_3$	73·5	10·4	16·1	72·7	10·2	15·8
(Vn)	194—197/0·2	66	$C_{18}H_{29}N_2O$	71·49	9·6	13·8	71·5	10·0	14·1
(Vo)	146—150/0·2	32	$C_{18}H_{31}N_3$	74·7	10·8	14·5	74·5	10·7	14·7
(Vp)	M.p.* 83—84°	26	$C_{18}H_{31}N_3O_2S$	61·2	8·8	11·9	61·8	9·0	11·4

* Needles from light petroleum (b.p. 60—80°). † Found Cl: 12·1%. Calc.: 12·6%. ‡ Found Cl: 12·4%. Calc.: 12·6%. § Found Br: 24·9. Calc.: 24·6%.

The compounds described herein were submitted for biological evaluation; none displayed sufficient activity to warrant further investigation.

EXPERIMENTAL

5′-Chloro-1,2-benzocyclohept-1-en-3-one (IIc).—This was prepared from 1-bromo-3-(*m*-chlorophenyl)propane [8] as for the preparation of the 6′-isomer.[3] The *ketone* had b.p. 110—113°/0·35 mm., (Found: Cl, 17·8. $C_{11}H_{11}ClO$ requires Cl, 18·2%) [*oxime*, needles (from ethanol) m.p. 128—131° (Found: C, 62·6; H, 5·8; Cl, 16·5. $C_{11}H_{12}ClNO$ requires C, 63·0; H, 5·8; Cl, 16·9%].

Oxidation of Ketone (IIc).—The ketone was oxidised with alkaline potassium permanganate to give 4-chlorophthalic acid (60%) as prisms from benzene–diethyl ether, m.p. 149—151° (lit.[11,12] 149—149·5°, 151°) (Found: C, 48·4; H, 2·7; Cl, 17·2. Calc. for $C_8H_5ClO_4$: C, 47·9; H, 2·5; Cl, 17·7). (The isomeric 3-chlorophthalic acid has a reported [13] m.p. of 186°).

4′-Chloro-1,2-benzocyclohept-1-en-3-one (IIf).—A solution of 4′-amino-1,2-benzocyclohept-1-en-3-one [5] (2·0 g., 0·012 mole) in water (40 ml.) and concentrated hydrochloric acid (20 ml.) was diazotised with a solution of sodium nitrite (0·82 g.) in water (5 ml.) at 0—5°. The diazonium solution was added as rapidly as possible to copper(I) chloride (3·25 g.) in concentrated hydrochloric acid (10 ml.) and the resulting mixture was heated to 35° for 5 min. The cooled mixture was extracted with ether to give the *4′-chloro-ketone* (1·18 g., 53%), b.p. 101°/0·15 mm. (Found:

[9] B. Belleau, *J. Medicin. Pharmaceut. Chem.*, 1959, **1**, 343.
[10] R. Huisgen and W. Rapp, *Ber.*, 1952, **85**, 826.
[11] M. Hayashi and I. Furusawa, *J. Soc. Chem. Ind., Japan*, 1941, **44**, 450 (*Chem. Abs.*, 1951, **45**, 1544).
[12] K. v. Auwers and L. Harres, *Z. phys. Chem.*, 1929, **143**, 1 (*Chem. Abs.*, 1930, **24**, 2108).
[13] J. C. Smith, *J. Chem. Soc.*, 1933, 1643.

C, 67·9; H, 5·7; Cl, 18·3. $C_{11}H_{11}ClO$ requires C, 67·9; H, 5·7; Cl, 18·2%), oxime, m.p. 139—141°.

3,4,5,6-*Tetrahydrobenz*[b]*azocine*-2(1H)-*one* (IIIa).—Sulphuric acid (*d* 1·84; 22 ml.) was added all at once to a suspension of 1,2-benzocyclohept-1-en-3-one oxime [14] (11·0 g., 0·63 mole) in glacial acetic acid (11 ml.). The temperature rose to 160—170°. The brown solution was allowed to cool to room temperature and was then poured into ice–water (*ca.* 200 ml.); the pH of the solution was adjusted to 11 with 10N-sodium hydroxide to give the lactam (9·6 g., 88%), m.p. 151—153° (lit.[2] m.p. 154—155°).

The following were prepared similarly: 7-*chloro*-3,4,5,6-*tetrahydrobenz*[b]*azocin*-2(1H)-*one* (IIIb, 85%) prisms (from aqueous ethanol), m.p. 198—199° (Found: C, 62·4; H, 5·97; Cl, 16·9. $C_{11}H_{12}ClNO$ requires C, 63·0; H, 5·8; Cl, 16·9%); 8-*chloro*-3,4,5,6-*tetrahydrobenz*[b]*azocin*-2(1H)-*one* (IIIc) (90%), prisms (from propan-2-ol), m.p. 163—166° (Found: C, 62·7; H, 5·8; Cl, 17·2. $C_{11}H_{12}ClNO$ requires C, 63·0; H, 5·8; Cl, 16·9%); and 9-*chloro*-3,4,5,6-*tetrahydrobenz*[b]*azocin*-2(1H)-*one* (III g.) (50%), prisms (from acetone), m.p. 191—193·5° (Found: C, 63·1; H, 5·9; N, 6·7. $C_{11}H_{12}ClNO$ requires C, 63·0; H, 5·8; N, 6·7%). [This compound was identical with that obtained by the Sandmeyer reaction on 9-amino-3,4,5,6-hexahydrobenz[*b*]azocine-2(1*H*)-one (IIIf)].

The m.p.s of these three isomeric chloro-compounds were depressed on admixture with either of the two other isomers.

Hydrolysis of the lactams with concentrated hydrochloric acid, diazotisation, and treatment with β-naphthol gave brilliant orange-red dyes.

9-*Nitro*-3,4,5,6-*tetrahydrobenz*[b]*azocin*-2(1H)-*one* (IIIe).—(*a*) Nitric acid (*d* 1·42; 50 ml.) was added during 90 min. to a stirred suspension of 3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-one (48·6 g., 0·28 mole) in sulphuric acid (*d* 1·84; 130 ml.), the temperature being maintained below 10° by external cooling. After the addition was completed, the mixture was allowed to reach room temperature (1 hr.) and was then poured into ice–water (400 ml.) to give the 9-*nitro-compound* (17·9 g., 29%) as cream-coloured needles (from ethanol), m.p. 211—212° (Found: C, 60·1; H, 5·5; N, 12·8. $C_{11}H_{12}N_2O_3$ requires C, 60·0; H, 5·5; N, 12·7%).

(*b*) 4-Nitro-1,2-benzocyclohept-1-en-3-one [5] was converted by the Schmidt reaction, as described for the 6-membered homologue by Smith and Berry,[4] into 9-nitro-3,4,5,6-hexahydrobenz[*b*]azocin-2(1*H*)one, m.p. [and mixed m.p. with the product obtained by method (*a*)] 209—211° (Found: C, 60·0; H, 5·5; N, 12·8. $C_{11}H_{12}N_2O_3$ requires C, 60·0; H, 5·5; N, 12·7%).

Degradation of 9-*Nitro*-3,4,5,6-*tetrahydrobenz*[b]*azocin*-2(1H)-*one* (IIIe).—A mixture of the 9-nitro-lactam (0·45 g.) and 2N-hydrochloride acid (10 ml.) was heated under reflux for 1 hr. The cooled solution was treated portionwise at 0—5° with sodium nitrite (0·14 g.). A small portion of this solution gave a bright orange dye with β-naphthol. The remaining volume of solution was treated with hypophosphorous acid [31% (w/w), 20 ml.] at 0° and the mixture was kept at this temperature for 2 hr. during which time nitrogen was evolved and a yellow precipitate of 5-(*p*-nitrophenyl)valeric acid (0·34 g., 71%) was formed. Recrystallisation from benzene–light petroleum (b.p. 60—80°) afforded pale-yellow needles, m.p. 83—85°, undepressed on admixture with an authentic specimen [6] (Found: C, 59·4; H, 5·9; N, 6·3. Calc. for $C_{11}H_{13}NO_4$: C, 59·2; H, 5·9; N, 6·3%).

9-*Amino*-3,4,5,6-*tetrahydrobenz*[b]*azocin*-2(1H)-*one* (IIIf).—A solution of 9-nitro-3,4,5,6-tetrahydrobenz[*b*]azocin-2(1H)-one (23·5 g., 0·107 mole) in methanol (350 ml.) was hydrogenated at 35° and 80 lb./in.^{2} in the presence of 5% palladium–charcoal. Filtration followed by evaporation of the solvent from the filtrate gave the 9-*amino-compound* (18·1 g., 89%), prisms from ethanol, m.p. 206—208° (Found: C, 69·3; H, 7·8; N, 14·2. $C_{11}H_{14}N_2O$ requires C, 69·5; H, 7·4; N, 14·7%).

9-*Chloro*-3,4,5,6-*tetrahydrobenz*[b]*azocin*-2(1H)-*one* (IIIg).—A solution of sodium nitrite (3·75 g.) in water (10 ml.) was added dropwise during 20 min. to a stirred solution of 9-amino-3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-one (10 g., 0·053 mole) in concentrated hydrochloric acid (50 ml.) at 0—5°. The diazonium solution was added as rapidly as possible to copper(I) chloride (15 g.) in concentrated hydrochloric acid (50 ml.) at 0°. The temperature rose spontaneously to 20°; it was then warmed to 35° for 5 min. to complete the reaction. 9-*Chloro*-3,4,5,6-*tetrahydrobenz*[b]*azocin*-2(1H)-*one* (9·5 g., 87%) was filtered off and crystallised from methanol to give prisms, m.p. 193—194° (Found: C, 62·7; H, 5·9; Cl, 16·8. $C_{11}H_{12}ClNO$ requires C, 63·0; H, 5·8; Cl, 16·9%). [This compound was identical with that obtained by Beckmann rearrangement of the oxime of 4′-chloro-1,2-benzocyclohept-1-en-3-one (IIf).

3-*Chloro*-N-*methyl*-N-*prop*-2-*ynylpropylamine*.—Prop-2-ynyl bromide (102 g., 1·06 mole) was added dropwise during 30 min. to a stirred mixture of 3-methylaminopropan-1-ol [15] (71·6 g., 0·8 mole) and anhydrous sodium acetate (93·8 g., 1·1 mole) in anhydrous acetone (850 ml.). After the addition was completed, the stirred mixture was heated under reflux for 22 hr., cooled, and filtered. Distillation of the filtrate afforded 3-hydroxy-*N*-methyl-*N*-prop-2-ynylpropylamine (32·8 g.) as a pale-yellow oil, b.p. 100—104°/14 mm.

A solution of thionyl chloride (62 g., 0·52 mole) in anhydrous benzene (75 ml.) was added dropwise during 45 min. to a stirred solution of the amino-alcohol (32·8 g., 0·26 mole) in anhydrous benzene (225 ml.) at such a rate that the temperature was kept below 35°. After the addition was completed, the mixture was stirred at room temperature, treated with anhydrous chloroform (300 ml.), and was then heated under reflux for 30 min. The solution was cooled and the hydrochloride (27·9 g.) (prisms from propan-2-ol, m.p. 144—145°) was filtered off, dissolved in water and basified with 2N-sodium hydroxide to give 3-*chloro*-N-*methyl*-N-*prop*-2-*ynylpropylamine* (20 g., 17%), b.p. 66—67°/13 mm. (Found: C, 58·1; H, 8·3; N, 9·8. $C_7H_{12}ClN$ requires C, 57·7; H, 8·3; N, 9·6%).

1-*Chloro*-3-(4-*methylpiperazin*-1-*yl*)*propane*.—A mixture of 1-methylpiperazine (100 g., 1·0 mole) and 3-bromo-1-chloropropane (78·5 g., 0·5 mole) in dry benzene (500 ml.) was stirred at room temperature for 1 hr. and then heated under reflux for 3 hr. The cooled mixture was filtered and the filtrate was extracted with 2N-hydrochloric acid (3 × 120 ml.). The extract was made strongly basic with 10N-sodium hydroxide and was then extracted with ether to give 1-*chloro*-3-(4-*methylpiperazin*-1-*yl*)*propane* (52·5 g., 60%), b.p. 136—140° (Found: Cl, 20·2; N, 16·1. $C_8H_{17}ClN_2$ requires Cl, 20·1; N, 15·9%).

General Procedure for the Preparation of 1-*Alkylaminoalkyl*-3,4,5,6-*tetrahydrobenz*[b]*azocin*-2(1H)-*ones*.—A stirred

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mixture of the lactam (III) (0·1 mole) and sodamide (4·3 g., 0·11 mole) in dry xylene (100 ml.) was heated under reflux in an atmosphere of dry nitrogen for 4 hr. The alkylaminoalkyl chloride (0·1 mole) was added and heating was continued for a further 20 hr. The mixture was cooled, and the xylene solution was distilled to give the required products (IV). The unsubstituted derivatives were purified (see Table 1) and the other derivatives were reduced to the corresponding azocines directly.

General Procedure for the Reduction of the Azocin-2-ones to Azocines.—A solution of the *N*-alkylaminoalkyl-3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-ones (IV) (0·1 mole) in dry ether (300 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (7·6 g., 0·2 mole) in dry ether (300 ml.) under dry nitrogen. The mixture was heated under reflux for 3 hr., the flask was cooled in ice, and water (*ca.* 20 ml.) was added cautiously to decompose the excess of hydride. The mixture was treated with 2N-sulphuric acid (250 ml.), the acidic layer was separated, tartaric acid (0·1 mole) was added to prevent the formation of insoluble salts, and the pH was adjusted to 11 with 10N-sodium hydroxide. Extraction with ether gave the 1-alkylaminoalkyl-1,2,3,4,5,6-hexahydrobenz[*b*]azocines (V) (see Table 2).

1-[3-(N-*Ethoxycarbonyl*-N-*methylamino*)*propyl*]-1,2,3,4,5,6-*hexahydrobenz*[b]*azocine* (Vj).—A solution of 1-(3-dimethylaminopropyl)-1,2,3,4,5,6-hexahydrobenz[*b*]azocine (7·0 g., 0·0284 mole) in dry benzene (50 ml.) was added dropwise to a stirred solution of ethyl chloroformate (3·6 g., 0·033 mole) in anhydrous benzene (50 ml.) at 40°. The mixture was then stirred and heated under reflux for 9 hr.; the cooled solution was extracted with 2N-hydrochloric acid (3 × 30 ml.). The acidic extract was basified with 10N-sodium hydroxide and extraction with ether gave 1-[3-(N-*ethoxycarbonyl*-N-*methylamino*)*propyl*]-1,2,3,4,5,6-*hexahydrobenz*[b]*azocine* [(Vj) Table 2)].

1-(3-*Methylaminopropyl*)-1,2,3,4,5,6-*hexahydrobenz*[b]*azocine* (Vk).—A mixture of the *N*-ethoxycarbonyl-*N*-methylamino-compound (Vj) (3·2 g., 0·0105 mole) and powdered potassium hydroxide (3·5 g., 0·062 mole) in carbitol (30 ml.) was heated gently under reflux for 6 hr. Water (250 ml.) was added to the cooled mixture and extraction with ether gave the *N*-methylamino-compound [(Vk) Table 2].

1-(3-*Dimethylaminopropyl*)-9-*nitro*-1,2,3,4,5,6-*hexahydrobenz*[b]*azocine* (VI).—1-(3-Dimethylaminopropyl-1,2,3,4,5,6-hexahydrobenz[*b*]azocine (20·2 g., 0·082 mole) was added dropwise during 30 min. to sulphuric acid (*d* 1·84; 50 ml.), the temperature being kept below 10° by external cooling. This mixture was treated with concentrated nitric acid (*d* 1·42; 20 ml.) dropwise at 0—5°. The mixture was stirred at this temperature for 2 hr. and was then poured into ice–water (500 ml.). The solution was basified with 10N-sodium hydroxide to give the 9-*nitro-compound* [(Vl): Table 2].

9-*Amino*-1-(3-*dimethylaminopropyl*)-1,2,3,4,5,6-*hexahydrobenz*[b]*azocine* (Vm).—A solution of the 9-nitro-compound (Vl), (32 g., 0·11 mole) in ethanol (200 ml.) was hydrogenated at 28° and 70 lb./in.² in the presence of 5% palladium–charcoal. Filtration, followed by distillation of the filtrate afforded the 9-*amino-compound* [(Vm): Table 2]; N-*acetyl-derivative* [(Vn): Table 2].

9-*Chloro*-1-(3-*dimethylaminopropyl*)-1,2,3,4,5,6-*hexahydrobenz*[b]*azocine* (Vh).—The 9-amino-compound (Vm) (5·0 g., 0·019 mole) was diazotised and the diazonium solution was added to copper(I) chloride (5·5 g.) in concentrated hydrochloric acid (50 ml.). After being warmed to 35° for 15 min. the mixture was poured into water (500 ml.). The solution was basified and extraction with ether gave the 9-*chloro-compound* [(Vh): Table 2], b.p. 136—140°/0·1 mm. This product had a g.l.c. retention time (23·4 min.) and i.r. spectrum identical with those of the product obtained from 9-chloro-3,4,5,6-tetrahydrobenz[*b*]azocin-2(1*H*)-one (IIIg) by the general procedure.

Gas Chromatographic Examination of the Chloro-1-(3-*dimethylaminopropyl*-1,2,3,4,5,6-*hexahydrobenz*[b]*azocines.*—The examination was carried out on a Perkin-Elmer 452 Gas Chromatograph with a 2 m. 5% Apiezon L–6% sodium hydroxide on Embacel (60—100 mesh) column at 170° and inlet pressure of 15 lb./in.² The retention time of (Vf) was 24·0 min., of (Vg) 26·4 min., and of (Vh) 23·4 min.

1-(3-*Dimethylaminopropyl*)-9-*ethylamino*-1,2,3,4,5,6-*hexahydrobenz*[b]*azocine* (Vo).—9-Acetamido-1-(3-dimethylaminopropyl)-1,2,3,4,5,6-hexahydrobenz[*b*]azocine (Vn) was reduced with lithium aluminium hydride similarly to the reduction of benz[*b*]azocin-2(1*H*)-ones to benz[*b*]azocines to give the desired 9-*ethylamino-compound* [(Vo): Table 2].

1-(3-*Dimethylaminopropyl*)-9(?)-*dimethylsulphamoyl*-1,2,3,4,5,6-*hexahydrobenz*[b]*azocine* (Vp).—1-(3-Dimethylaminopropyl)-1,2,3,4,5,6-hexahydrobenz[*b*]azocine (3·7 g., 0·015 mole) was added dropwise to stirred chlorosulphonic acid (10 ml.) at 0°. The mixture was stirred at room temtemperature for 30 min.and then at 100° for 4 hr.; it was then poured onto crushed ice. The mixture was basified with 40% aqueous dimethylamine solution and extracted with benzene (3 × 75 ml.). Evaporation of the dried ($MgSO_4$) extract gave an oily residue which was heated with an excess of 40% aqueous dimethylamine solution at 100° for 10 min. The solution was concentrated under reduced pressure and the residue was extracted with ether to give the 9(?)-*dimethylsulphamoyl derivative* [(Vp) Table 2].

9(?)-*Dimethylsulphamoyl*-3,4,5,6-*tetrahydrobenz*[b]*azocin*-2(1H)-*one* (IIIh) (33%) prisms (from ethanol), m.p. 215—216°, (Found: N, 9·7; S, 11·2. $C_{13}H_{18}N_2O_2S$ requires N, 9·9; S, 11·4%) was prepared similarly.

1-(3-*Dimethylaminopropionyl*)-1,2,3,4,5,6-*hexahydrobenz*-[b]*azocine* (VIII).—β-Chloropropionyl chloride (6·0 g., 0·047 mole) was added dropwise during 10 min. to a stirred solution of 1,2,3,4,5,6-hexahydrobenz[*b*]azocine [8] (7·0 g., 0·043 mole) in dry benzene (30 ml.) at 20—30°. After the addition was completed, the mixture was stirred at room temperature for 1 hr. and was then poured carefully into an excess of saturated aqueous sodium hydrogen carbonate. Separation of the benzene layer and evaporation of the solvent afforded the 1-(3-chloropropionyl) derivative (VII) (6·6 g.), m.p. 82·5—84·5°. This was heated with a solution of dimethylamine (25·3 g.) in dry toluene (30 ml.) in a stainless-steel bomb at 100° for 10 hr. The cooled mixture was diluted with ether (300 ml.), the dimethylamine hydrochloride was filtered off, and the filtrate was evaporated to give the 1-(3-*dimethylaminopropionyl*) *compound* (5·6 g., 84%), b.p. 136—137°/0·16 mm. (Found: C, 73·2; H, 9·3; N, 10·7. $C_{16}H_{24}N_2O$ requires C, 73·8; H, 9·3; N, 10·8%.

1-*Amino*-3-(4-*hydroxypiperidino*)*propane* (XIIc).—A mixture of 4-hydroxypiperidine (50·5 g., 0·5 mole) and acrylonitrile (26·5 g., 0·5 mole) in ethanol (250 ml.) was heated under reflux for 2 hr.; it was then distilled to give 1-(2-cyanoethyl)-4-hydroxypiperidine (60 g.), b.p. 160—166°/5 mm. This was hydrogenated in ethanolic ammonia solution (300 ml.) over Raney nickel at 50° and 650 lb./in.²

to give 3-(4-*hydroxypiperidino*)*propylamine* (26 g., 33%), b.p. 99—102°/0·06 mm. (Found: C, 60·6; H, 11·7; N, 16·9. $C_8H_{18}N_2O$ requires C, 60·7; H, 11·5; N, 17·7%).

3-(3-*Dimethylaminopropyl*)-1,2,3,4,5,6-*hexahydrobenz*[d]-*azocine* (X).—As described in the general procedure for alkylaminoalkylation of benz[*b*]azocin-2(1*H*)-ones, 1,2,5,6-tetrahydrobenz[*d*]azocin-4(3*H*)-one [2] (3·5 g., 0·02 mole) was treated with 3-dimethylaminopropyl chloride (2·66 g., 0·022 mole) in dry xylene and the crude product (4·91 g.) was reduced with lithium aluminium hydride in dry ether to give 3-(3-*dimethylaminopropyl*)-1,2,3,4,5,6-*hexahydrobenz*[d]-*azocine* (1·9 g., 41%), b.p. 103·5—104°/0·05 mm. (Found: C, 77·5; H, 10·5; N, 11·8. $C_{16}H_{26}N_2$ requires C, 78·0; H, 10·6; N, 11·4%).

2-(3-*Dimethylaminopropyl*)-1,2,3,4,5,6-*hexahydrobenz*[c]-*azocine* (XIIIa).—A stirred mixture of 4-(*o*-chloromethylphenyl)butyl chloride [9] (7·8 g., 0·036 mole), 3-dimethylaminopropylamine (5·5 g., 0·054 mole), anhydrous lithium bromide (6·25 g., 0·072 mole), and anhydrous potassium carbonate (2·5 g., 0·018 mole) in n-butanol (50 ml.) was heated under reflux for 16 hr. The n-butanol was distilled off under reduced pressure, water (75 ml.) was added to the residue, and the solution was acidified with 2N-sulphuric acid (100 ml.). The solution was washed once with ether (100 ml.) and the pH of the acidic solution was adjusted to 11 with 10N-sodium hydroxide. Extraction with chloroform gave 2-(3-*dimethylaminopropyl*)-1,2,3,4,5,6-*hexahydrobenz*[c]*azocine* (2·1 g., 24%), b.p. 119—121°/0·15 mm. (Found: C, 78·0; H, 10·8; N, 11·4. $C_{16}H_{26}N_2$ requires C, 78·0; H, 10·6; N, 11·4%); *dihydrochloride*, prisms (from ethanol–diethyl ether), m.p. 238—240° (Found: Cl, 22·1; N, 8·6. $C_{16}H_{26}N_2$,2HCl requires Cl, 22·2; N, 8·8%).

The following were prepared similarly: 2-(3-*dimethylamino*-2-*methylpropyl*)-1,2,3,4,5,6-*hexahydrobenz*[c]*azocine* (XIIIb) (22%), b.p. 120—128°/0·5 mm. (Found: C, 78·4; H, 10·5; N, 10·4. $C_{17}H_{28}N_2$ requires C, 78·4; H, 10·8; N, 10·8%); and 2-[3-(4-*hydroxypiperidino*)*propyl*]-1,2,3,4,5,6-*hexahydrobenz*[c]*azocine dihydrochloride* (XIIIc) (8%), prisms from ethanol–diethyl ether, m.p. 244—247° (Found: C, 60·0; H, 8·5; Cl, 19·1. $C_{19}H_{30}N_2O$,2HCl requires C, 60·8; H, 8·6; Cl, 18·9%).

3-(3-*Dimethylaminopropyl*)-3-*hydroxy*-1,2-*benzocyclo-oct*-1-*ene* (XVI).—A solution of 1,2-benzocyclo-oct-1-en-3-one [10] (5·0 g., 0·029 mole) in dry tetrahydrofuran (10 ml.) was added dropwise during 10 min. to a stirred suspension of 3-dimethylaminopropylmagnesium chloride [16] [from 1-chloro-3-dimethylaminopropane (5·3 g., 0·044 mole) and magnesium (1·06 g., 0·044 g.-atom)] in dry tetrahydrofuran (20 ml.). The stirred mixture was heated under reflux for 5 hr.; the cooled mixture was then poured into a solution of ammonium chloride (8·5 g.) in water (125 ml.) and immediately extracted with ether (3 × 100 ml.). The combined extracts were washed with 2N-acetic acid (3 × 75 ml.) and the acid solution was basified with 10N-sodium hydroxide to give the *alcohol* (0·8 g., 11%), b.p. 165—168°/0·8 mm. (Found: C, 78·0; H, 10·3; N, 5·3. $C_{17}H_{27}NO$ requires C, 78·1; H, 10·4; N, 5·4%).

3-(3-*Dimethylaminopropyl*)-1,2-*benzocyclo-oct*-1-*ene* (XVII).—A stirred mixture of 3-hydroxy-3-(3-dimethylaminopropyl)-1,2-benzocyclo-oct-1-ene (1·06 g., 0·004 mole) and anhydrous sodium acetate (1·06 g., 0·013 mole) in acetic anhydride (6·5 ml.) was heated under reflux for 3 hr. The mixture was poured into ice–water (50 ml.), the pH was adjusted to 11 with 10N-sodium hydroxide, and extraction with ether gave a 1 : 2 : 5 mixture of isomeric di-olefins (0·42 g.), b.p. 154—158°/1·0 mm. (Found: C, 83·4; H, 10·2; N, 5·8. $C_{17}H_{25}N$ requires C, 83·9; H, 10·4; N, 5·8%). The mixture was hydrogenated in ethanol (50 ml.) over 5% palladium–charcoal at 80° and 500 lb./in.^{2} to give 3-(3-*dimethylaminopropyl*)-1,2-*benzocyclo-oct*-1-*ene* (0·196 g., 47%), b.p. 135—139°/0·35 mm. (Found: C, 83·0; H, 11·2; N, 5·7. $C_{17}H_{27}N$ requires C, 83·2; H, 11·1; N, 5·7%).

The authors thank S. Bance and his staff for microanalyses and i.r. spectra, R. Philo for gas chromatographic analyses, and A. P. Flynn, S. J. Griffiths, R. J. Hollingbery, and E. H. Smith for technical assistance.

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[9/831 *Received, May 19th*, 1969]