

## The Schmidt Reaction with Oxa- and Azabenzocycloalkenones

D. Misiti, V. Rimatori (1) and F. Gatta

Laboratori Chimica Terapeutica, Istituto Superiore Sanità, Rome Italy

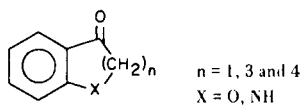
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Five, seven and eight membered ring oxa- and azabenzocycloalkenones were submitted to the Schmidt reaction and the ratio of the respective isomeric rearrangement products have been determined and compared with that of six membered ring oxa- and azabenzocycloalkenones.

It has been stated that the Schmidt reaction with aryl, alkyl, and cycloalkenyl ketones, including acetophenone, 1'- and 2'-acetophenone and 1-tetralone, gives almost exclusively *N*-arylamides as a result of aryl migration (2,3). However, in the Schmidt reaction in sulfuric acid with 1-indanone containing a methoxy substituent *para* or *ortho* to the carbonyl group an alkyl migration has been demonstrated (4). More recently it has been found that the Schmidt reaction with 4-chromanones (5) and flavanones (6), did not give 2,3-dihydro-1,5-benzoxazepin-4(5*H*)ones as major compounds, but rather, the isomeric lactams, 2,3-dihydro-1,4-benzoxazepin-5(4*H*)ones. Similarly, we have shown that under the same conditions 1,2,3,4-tetrahydroquinolin-4-ones (7) yield as a major compound 1,2,3,4-tetrahydro-1,4-benzodiazepin-5(4*H*)ones as a result of alkyl migration, due to the electronic effects of the presence of the hetero atom *ortho* to the carbonyl group.

A paper by Uyeo *et al.* (8) has shown that the ratio of the directions of migration in the Schmidt reaction with benzocycloalkenones possessing a rigid and nearly planar structure are affected by the electronic effects of the substituents of the aromatic ring in the positions *para* or *ortho* to the carbonyl group, leading to a predominant alkyl migration. With an increase in flexibility of the alicyclic ring, the electronic effects of substituents in the aromatic ring decrease, resulting in an increase of aryl migration closely approximating that of acetophenones.

The present paper deals with an examination of the alkyl and aryl migrations of heterocyclic ketones with the general formula in the Schmidt reaction.

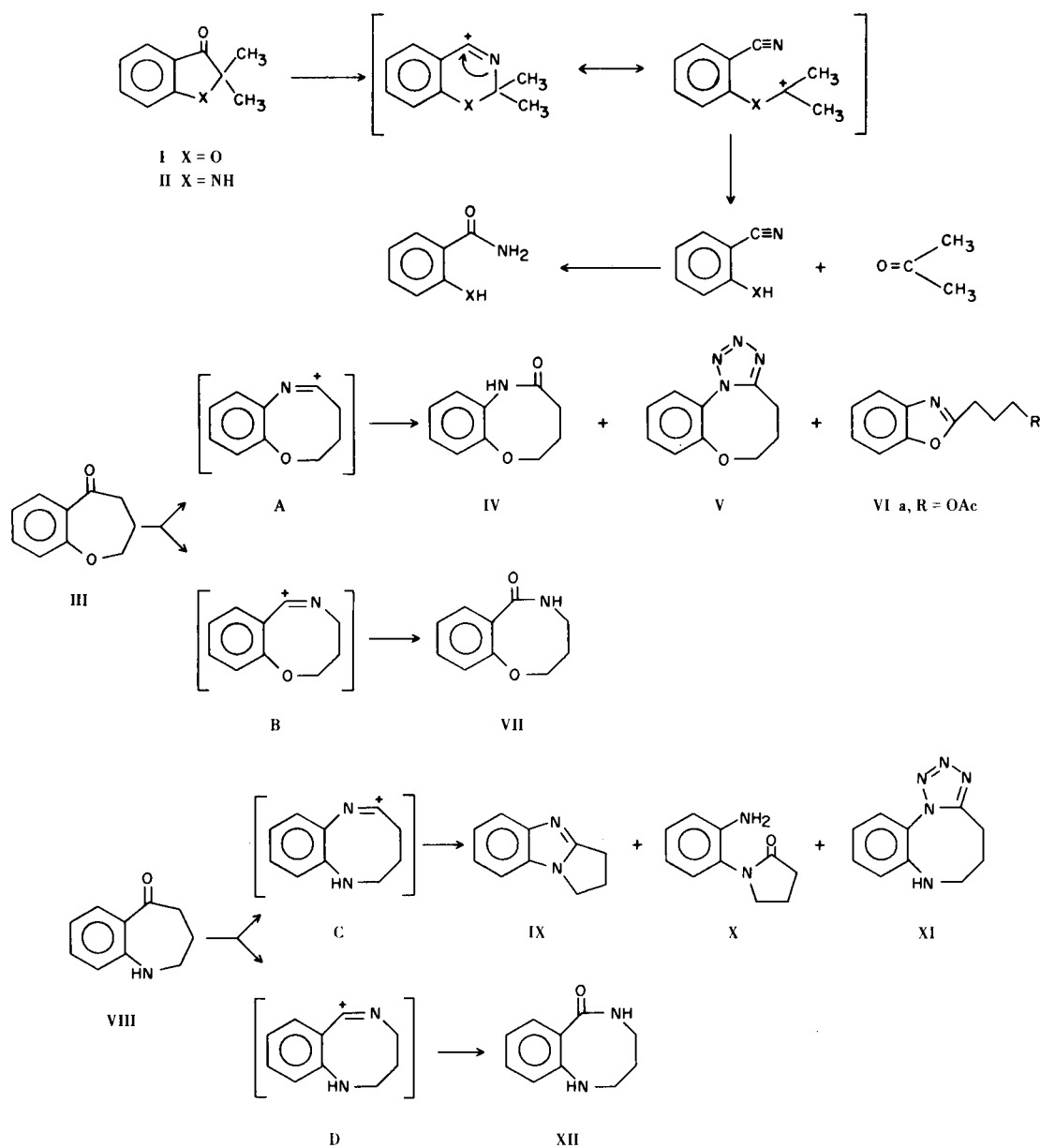


The reaction was applied to the 2,2-dimethyl-3(2*H*)-benzofuranone (I) (9) and 2,2-dimethyl-3-indolinone (II) (10) as five membered heterocyclic ketones, and to the 3,4-dihydro-2*H*-1-benzoxepin-5-one (III) (11) and 1,2,3,4-tetrahydro-1-benzazepin-5-one (VIII) (12a) (and the related *N*-tosyl derivative (VIIIa) (12b)) as seven membered heterocyclic ketones and finally to the 2,3,4,5-tetrahydro-1*H*-1-benzazocin-6-one (XIII) (and related *N*-tosyl (XIIIa) and *N*-acetyl (XIIIb) derivatives) as eight membered heterocyclic ketones.

2,2-Dimethyl-3(2*H*)-benzofuranone (I) and 2,2-dimethyl-3-indolinone (II) were selected instead of the unsubstituted compounds 3(2*H*)-benzofuranone and 3-indolinone because the latter are unstable under experimental conditions. Ketones I and II with sodium azide in sulfuric acid are readily converted to salicylonitrile (51%) and salicylamide (29%) and anthranilic nitrile (88%) and anthranilamide (6%), respectively, by the proposed mechanism.

Acetone was detected by glc in both reactions. The foregoing results indicate that the migration is almost exclusively of the alkyl type in the case of the Schmidt reaction with five membered heterocyclic ketones. However, it has been reported that isatin rearranges to 1*H*,3*H*-quinazoline-2,4-dione as a result of an alkyl migration (13).

When 3,4-dihydro-1-benzoxepin-5(2*H*)one (III) was subjected to the Schmidt reaction in a sulfuric-acetic acid mixture, we isolated 3,4-dihydro-2*H*-1,6-benzoxazocin-5(6*H*)one (IV) (ca. 54%), a related tetrazole derivative, 4,5-dihydro-6*H*-tetrazolo[5,1-*e*]-1,6-benzoxazocine (V) (ca. 4%) together with 2-(3-acetoxy-propyl)benzoxazole (VIa) (ca. 13%) by aryl migration and 2,3,4,5-tetrahydro-1,5-benzoxazocin-6-one (VII) (ca. 5%) formed by alkyl migration. Benzoxazole VIa is possibly formed by reaction of acetic acid on the intermediate carbonium ion (A), followed by an intramolecular rearrangement.

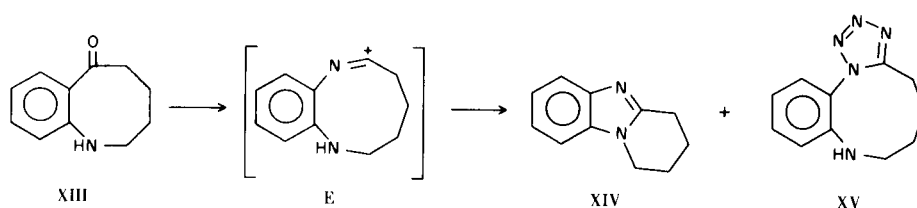


Recently, it has been reported that the Schmidt reaction in sulfuric acid on the 8-chloro-3,4-dihydro-1-benzoxepin-5(2*H*)one yields only 9-chloro-4,5-dihydro-6*H*-tetrazolo-[5,1-*e*]-1,6-benzoxazocine (ca. 22.5%), by aryl migration (14).

Aryl migration is predominant in the Schmidt rearrangement of 1,2,3,4-tetrahydro-1-benzazepin-5-one (VIII), giving 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole (IX) (15) (ca. 65%) and *N*-(2-aminophenyl)-2-pyrrolidone (X) (16) (ca. 8%), both obtained *via* the intramolecular rearrangement of the intermediate carbonium ion (C), and the tetrazole derivative, 4,5,6,7-tetrahydro-1,5-benzodiazocin-6-one (XII) (ca. 2%).

The reaction carried out on the *N*-tosyl derivative (VIIIa) (12b) gave similar compounds in comparable yields; in addition, the 1-tosyl-derivative (XIa) (ca. 3%) was isolated.

Only aryl migration has been observed in the Schmidt reaction with 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazocin-6-one (XIII). The 1,2,3,4-tetrahydropyrrolo[1,2-*a*]benzimidazole (XIV) (15a,b; 17) (ca. 54%), possibly obtained *via* the intramolecular rearrangement of the intermediate



carbonium ion (E), as well as the tetrazole derivative, 4,5,6,7-tetrahydro-8*H*-tetrazolo[5,1-*f*]-1,7-benzodiazonine (XV) (ca. 23%), were isolated.

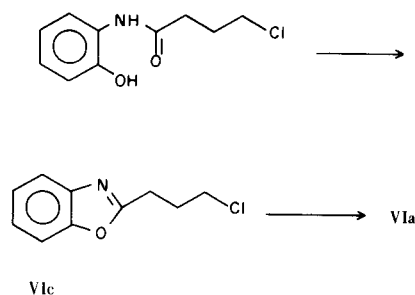
Similarly the reactions carried out on the *N*-tosyl (XIIIa) and *N*-acetyl (XIIIb) derivatives gave the same compounds in comparable yields.

These results are summarized and compared to the results on six membered heterocyclic ketones in Table I.

In view of the above facts, the most reasonable conclusion to be drawn is that the ratio of the directions of migration in the Schmidt reaction with benzoheterocyclic ketones possessing a rigid and nearly planar structure, *i.e.*, five-membered cyclic ketones I and II or six membered such as 4-chromanone, flavanone, and 1,2,3,4-tetrahydroquinolin-4-one, is influenced by the electronic effects of the hetero atom *ortho* to the carbonyl group. The migration is predominantly of the alkyl type. Conversely, the increase in flexibility of the heterocyclic ring of seven membered cyclic ketones III and VIII results in a strong enhancement of the ratio of aryl migration. In the case of the eight membered cyclic ketones XIII only aryl migration occurs and no compound arising from an alkyl migration could be detected. These conclusions are in agreement with those observed by Uyeo for benzocycloalkenones with electron-releasing substituents *ortho* or *para* to the carbonyl group.

#### Structural Assignment.

Salicylonitrile, salicylamide, anthranilic nitrile and anthranilamide obtained from the Schmidt reaction on compounds I and II were identical to authentic samples of these compounds. The assignment of structure VIa that follows is derived from chemical and spectral evidence. The structure of an ester was shown by obtaining an alcohol VIb by mild alkaline hydrolysis of VIa. Compound VIa was also synthesized by the following route:



*o*[*N*( $\gamma$ -chlorobutyrylamino)]phenol (18) was cyclized to 2-(3-chloropropyl)benzoxazole (VIc) by phosphorus pentoxide, which undergoes a nucleophilic attack by the acetate ion to give VIa.

The structure of the two isomeric lactams IV and VII is supported by chemical and spectral evidence. Com-

TABLE I

Ketones	Yield %	Isomer ratio	
		% Aryl migration	% Alkyl migration
2,2-Dimethyl-3(2 <i>H</i> )benzofuranone (I)	80	-----	100
2,2-Dimethyl-3-indolinone (II)	94	-----	100
4-Chromanone (5c)	78	-----	100
Flavanone (6)	91	3	97
1,2,3,4-Tetrahydro-quinolin-4-one (7)	88	20	80
3,4-Dihydro-1-benzoxepin-5(2 <i>H</i> )one (III)	76	93	7
1,2,3,4-Tetrahydro-1-benzazepin-5-one (VIII)	81	97	3
2,3,4,5-Tetrahydro-1 <i>H</i> -1-benzazocin-6-one (XIII)	77	100	-----

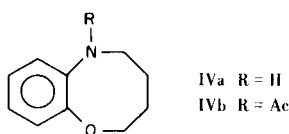
TABLE II

## Rearrangement Products and Related Compounds

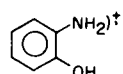
	M.p. °C Recryst. Solv. (B.p. °C/mm Hg)	NH, amid. (OH)	NH, amin. (OH)	NMR ( $\delta$ )		-CH <sub>2</sub> -(X)	-C-CH <sub>2</sub> -C-	-CH <sub>3</sub>	$\nu$ NH,OH	$\nu$ CO
IV	159-160 AcOEt-hexane	8.47 b		7.10 b		4.20 t (OAr) 2.30 m (C=O)	2.00 m		3311	1658
IVa	(55-60/0.05)	(a)	3.50 b	6.90-6.23 m		4.00 m (OAr) 3.50 m (NH)	1.70 m (4H)		3333 (b)	
IVb	(65-70/0.05)			7.20 b		4.10 b (OAr) 3.00 ca. b (NAc)	1.70 m (4H)	1.77 s (NAc)		
V	122-124 AcOEt			7.77-7.10 m		4.30 t (OAc) 3.13 t (C=N)	2.07 q			
VIa	35-36 (100-110/0.05)			7.83-7.17 m		4.23 t (OAc) 3.03 t (C=N)	2.25 q	2.00 s (OAc)		
VIb	unstable oil	(a)	(4.00 bs)	7.70-7.07 m		3.72 t (OH) 3.03 t (C=N)	2.08 q		3300 (b)	
VIc	(55-58/0.05)			7.70-7.00 m		3.63 t (Cl) 3.05 t (C=N)	2.28 q			
VII	114-114.5 water	7.40 b		7.63 dd (H-7) (c); 7.76-6.70 m		4.30 t (OAr) 3.35 m (NH)	1.95 m		3322	1635
XI	104-105 AcOEt-hexane		4.47 b	7.50-6.50 m		3.25 t (NH) 2.92 t (C=N)	1.90 q		3367	
XIa	208-209 AcOEt			7.90-7.30 m (8H)		4.40 t (NTs) 3.90 t (C=N)	2.10 m	2.40 s (arom.)		
XII	166-168 AcOEt-hexane	6.25 b	4.11 b	7.50 dd (H-7) (c); 7.30-6.40 m		3.43 m (d) (NH) (4H)	1.68 m		3310 (c)	1630
XIII	90-91 hexane		4.33 b	7.40 dd (H-7); 7.13 dt (H-9); 6.78 dd (H-8); 6.63 dd (H-10) (c)		3.13 t (NH) 2.80 t (C=O)	1.83 m (4H)		3320	1665
XIIIb	138-140 benzene			8.10 dd (H-7) (c); 7.73-7.03 m		3.90 b (NAc) 3.00 t (C=O)	1.80 m (4H)	1.82 s (NAc)		1660 b
XV	130-131		3.90 b	7.60-6.40 m		2.67 m (d) (NH) 3.03 t (C=N)	1.83 m (4H)		3378	

(a) Solvent: carbon tetrachloride; (b) film; (c) observed: J, ortho 8 cps, J, meta 2 cps; (d) triplet on addition of deuterium oxide; (e) Nujol.

parison of the ir carbonyl absorption of IV (19) and VII showed a small but significant difference ( $23\text{ cm}^{-1}$ ) between the anilide (IV) which has the higher frequency, and the benzamide (VII). Nmr data also supports the structures assigned to the products. The difference between chemical shifts of the methylene group of IV ( $\delta\ 2.30$ ) and VII ( $\delta\ 3.35$ ) is in agreement with the view that a methylene, next to the carbonyl function in a lactam group, absorbs at a higher field when compared to a similar methylene group next to the NH-function of the lactam group (5d,6a,20). An additional way of distinguishing the isomeric lactams, is the presence in the nmr spectrum of VII of a single proton absorption at low field ( $\delta\ 7.63$  dd), assigned to the deshielded C-7 aromatic proton (5c,6a,7,21). The uv absorption spectrum of the reduction product of the lactam (IV) with LAH confirmed the assigned structures of the lactams. In fact, the uv spectrum of the amine (IVa) showed a hypsochromic shift on acidification of its alcoholic solution, indicating that the nitrogen atom is linked to the benzene ring (6a). This structure was also characterized by its *N*-acetyl derivative (IVb).

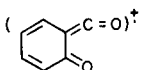


The patterns of fragmentation by electron impact on the two isomeric benzoxazocinones (IV) and (VII) are very different. The most significant peaks in the mass spectra of IV is  $m/e\ 109$



and VII are  $m/e\ 148$

( $M^+ - 29$ ) (22), and  $m/e\ 120$

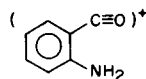


The structure of

the tetrazole (V) was elucidated by LAH reduction of the tetrazole ring (6a,23) to give benzoxazocinone (IVa). The structure of compound IX was identical to the authentic sample (15); similarly compound X and its LAH reduction product was assigned the structure of *N*-(2-aminophenyl)-2-pyrrolidone (16) and *N*-(2-aminophenyl)pyrrolidine (24) respectively by comparison with the authentic samples obtained by an independent method.

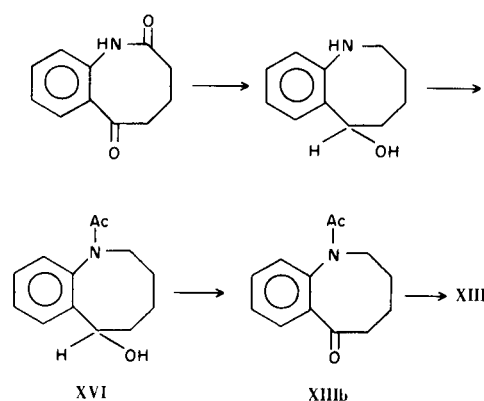
Structural assignment for the lactam XII was made, as shown before, for lactam VII. For example, the ir carbonyl absorption was  $1630\text{ cm}^{-1}$ ; the single proton nmr absorption at low field ( $\delta\ 7.50$  dd) was assigned to the deshielded C-7 aromatic proton. The major mass

spectral peaks were  $m/e\ 147$  ( $M^+ - 29$ ) (22) and  $m/e\ 119$



The structure of tetrazole XI was elucidated by LAH reduction of the tetrazole ring to give compound IX. Similarly, *N*-tosyl derivative of the tetrazole XI gave compound IX by LAH reduction.

2,3,4,5-Tetrahydro-1*H*-1-benzazocin-6-one (XIII), not previously described in the literature, was prepared in the following way:



3,4-Dihydro-1*H*-1-benzazocin-2,6(5*H*)dione (25) was reduced to give 1,2,3,4,5,6-hexahydro-1-benzazocin-6-ol (26), which, by acetylation followed by oxidation, yielded the *N*-acetyl derivative of XIII. Alkaline hydrolysis of the last compound gave the final product, benzazocinone (XIII).

The structure of compound XIV was identical to an authentic sample (17). Compound XV was found to have a tetrazole structure and gave the rearrangement product XIV after LAH reduction, as did the tetrazole XI.

Additional spectroscopic data are reported in Table II.

## EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus (uncorrected); ir spectra were recorded on a Perkin-Elmer model 21 double beam spectrophotometer, in chloroform solution unless otherwise stated. Nmr spectra were taken using a Varian T-60 spectrometer, in deuteriochloroform solution unless otherwise stated. Chemical shifts are measured in ppm ( $\delta$ ) using TMS as an internal standard. Peaks assigned to protons from  $\text{NHCO-}$ ,  $\text{NH-}$  and  $\text{OH}$  groups (Table II) disappeared after exchange in deuterium oxide. Thin layer chromatography studies were accomplished using plates of silica gel (Merck GF<sub>254</sub>).

Schmidt Reaction of Oxa- and Azabenzocycloalkenones. General Conditions.

Concentrated sulfuric acid (5 ml.) was added with cooling and stirring to a suspension of the heterocyclic ketones (I, II, III, VIII

and VIIIa, XIII, XIIIa and XIIIb) (ca. 1 g.) and sodium azide (0.5 g.) in glacial acetic acid (20 ml.). In general the reaction was complete after about 24 hours at room temperature. The reaction mixture was cooled and then neutralized with an aqueous solution of sodium carbonate and extracted with ethyl acetate. The combined extracts were dried over sodium sulfate and evaporated to give a crude residue which was chromatographed on silica gel column.

#### 2,2-Dimethyl-3(2H)benzofuranone (I) (9).

This compound was converted to a mixture of salicylonitrile and salicylamide in an 80% yield. The crude product was chromatographed on a silica gel column eluting with hexane gradually enriched with ethyl acetate. First, salicylonitrile, m.p. 102-104°, in a 51% yield and then practically pure salicylamide, m.p. 140-141°, in a 29% yield was obtained.

#### 2,2-Dimethyl-3-indolinone (II) (10).

This compound was converted to a mixture of anthranilic nitrile, and anthranilamide in a 94% yield. The crude product was chromatographed on a silica gel column eluting with mixtures of hexane-ethyl acetate with a gradual increase of ethyl acetate. First, the anthranilic nitrile, m.p. 49-50°, in an 88% yield and then pure anthranilamide, m.p. 113-114° in a 6% yield, was obtained. The two compounds isolated from these reactions were compared to authentic samples (mixed m.p.'s, ir and nmr spectra).

#### Schmidt Reaction on 3,4-Dihydro-1-benzoxepin-5-(2H)one (III) (11).

The crude residue was crystallized from ethyl acetate-hexane to give 3,4-dihydro-2H-1,6-benzoxazocin-5(6H)one (IV) (48% yield) practically pure. The pure compound was obtained after repeated recrystallization; mass spectrum: m/e (1%), 177 (18.6) M<sup>+</sup>, 135 (2.3), 120 (4.6), 109 (76.8), 106 (2.0), 93 (3.4), 92 (3.6), 91 (3.6), 80 (11.8), 69 (100), 65 (8.5), 52 (22.2), 45 (5.2), 41 (50.3), 39 (15.0), 28 (18.0), 18 (14.1).

*Anal.* Calcd. for C<sub>10</sub>H<sub>11</sub>NO<sub>2</sub>: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.77; H, 6.22; N, 8.04.

#### 2,3,4,5-Tetrahydro-6H-1,6-benzoxazocine (IVa).

This compound was obtained in good yield by LAH reduction of IV after heating under reflux in ether solution for 10 hours; uv: λ max (ethanol) 255 (log ε 4.02), 303 (log ε 3.37) nm; λ max (0.1 N hydrogen chloride/ethanol) 260 sh (log ε 2.75), 264 (log ε 2.83), 270 (log ε 2.79) nm.

*Anal.* Calcd. for C<sub>10</sub>H<sub>13</sub>NO: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.85; H, 8.11; N, 8.60.

#### N-acetyl-2,3,4,5-tetrahydro-1,6-benzoxazocine (IVb).

This compound was obtained by treatment of amine (IVa) with acetic anhydride-pyridine 10:1 for 12 hours at room temperature.

*Anal.* Calcd. for C<sub>12</sub>H<sub>15</sub>NO<sub>2</sub>: C, 70.22; H, 7.36; N, 6.82. Found: C, 70.12; H, 7.34; N, 6.60.

The residue from the mother liquors of crystallization of IV was chromatographed on a silica gel column. The column was first eluted with 1:3 ethyl acetate-hexane giving crude 2-(3-acetoxypropyl)benzoxazole (VIa) (13% yield), which was purified by vacuum distillation.

*Anal.* Calcd. for C<sub>12</sub>H<sub>13</sub>NO<sub>3</sub>: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.94; H, 5.95; N, 6.40.

#### 2-(3-Hydroxypropyl)benzoxazole (VIb).

This compound was obtained as an unstable oil by mild

alkaline hydrolysis (0.1 N sodium hydroxide in methanol at 5-10° for 24 hours). The crude product was purified by chromatography on silica gel column eluting with 1:1 ethyl acetate-hexane.

*Anal.* Calcd. for C<sub>10</sub>H<sub>11</sub>NO<sub>2</sub>: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.68; H, 6.20; N, 7.85.

Elution with 1:2 ethyl acetate-hexane yielded 4,5-dihydro-6H-tetrazolo[5,1-e]-1,6-benzoxazocine (V) (4% yield), purified by repeated recrystallization.

*Anal.* Calcd. for C<sub>10</sub>H<sub>10</sub>N<sub>4</sub>O: C, 59.39; H, 4.98; N, 27.71. Found: C, 59.36; H, 4.96; N, 27.82.

#### The Lithium Aluminum Hydride Reduction of Tetrazole (V).

The 1,6-benzoxazocine (IVa) was obtained in good yield by LAH reduction of the tetrazole (V) after heating under reflux in ether solution of 12 hours. The reduction product which resulted was identical with the benzoxazocine obtained by LAH reduction of IV (comparison of ir and nmr spectra) as shown above.

Elution with 1:1 ethyl acetate-hexane yielded an additional amount of the above benzoxazocinone (IV) (6% yield).

Finally elution with ethyl acetate gave practically pure 2,3,4,5-tetrahydro-1,5-benzoxazocin-6-one (VII) (5% yield), further purified by recrystallization; mass spectrum: m/e (1%), 177 (48.0) M<sup>+</sup>, 149 (7.4), 148 (22.1), 134 (22.1), 121 (43.0), 120 (100), 105 (3.7), 94 (4.1), 93 (7.4), 92 (43.0), 77 (3.1), 76 (3.7), 75 (3.1), 65 (6.1), 64 (13.5), 63 (10.4), 56 (13.5), 50 (4.1), 45 (4.9), 44 (30.7), 39 (9.2), 30 (9.2), 28 (22.1), 18 (19.7).

*Anal.* Calcd. for C<sub>10</sub>H<sub>11</sub>NO<sub>2</sub>: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.88; H, 6.15; N, 7.87.

#### 2-(3-Chloropropyl)benzoxazole (VIc).

A mixture of *o*[N(γ-chlorobutyroylamino)]phenol (18) (0.5 g.) and phosphorus pentoxide (0.2 g.) was heated at 110° with stirring for 1 hour. The reaction mixture was poured into an ice-cooled saturated sodium bicarbonate solution and finally extracted with ethyl acetate. The combined extracts were dried (sodium sulfate) and then evaporated. The crude product was chromatographed on a silica gel column eluting with 1:5 ethyl-acetate-hexane. Practically pure benzoxazole (VIc) was obtained, which was further purified by vacuum distillation (60% yield).

*Anal.* Calcd. for C<sub>10</sub>H<sub>10</sub>ClNO: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.21; H, 5.05; N, 7.24.

#### 2-(3-Acetoxypropyl)benzoxazole (VIa).

A mixture of VIc (120 mg.), potassium acetate (70 mg.) and sodium iodide (10 mg.) was heated at 100° for 5 hours. The reaction mixture was extracted with ethyl acetate and the combined extracts evaporated. The crude residue was chromatographed on a silica gel column eluting with 1:3 ethyl acetate-hexane. The crude benzoxazole (VIa) was obtained which was further purified by vacuum distillation. This product was identical with that above described under VIa comparison of the ir and nmr spectra.

#### The Schmidt Reaction on 1,2,3,4-Tetrahydro-1-benzazepin-5-one (VIII) (12a).

The crude residue was crystallized from ethyl acetate-hexane to give 2,3-dihydro-1H-pyrrolo[1,2-*a*]benzimidazole (IX) (48% yield), m.p. 114-115°, and was identical in all respects with an authentic sample (15).

The crude residue from the mother liquors of crystallization of IX was chromatographed on a silica gel column eluting with ethyl acetate.

4,5,6,7-Tetrahydro-tetrazolo[5,1-*e*]-1,6-benzodiazocine (XI).

This compound was first eluted and purified by recrystallization (6% yield).

*Anal.* Calcd. for  $C_{10}H_{11}N_5$ : C, 59.68; H, 5.55; N, 34.81. Found: C, 59.84; H, 5.53; N, 35.02.

## Lithium Aluminum Hydride Reduction of Tetrazole (XI).

The pyrrolbenzimidazole (IX) was obtained in good yield by LAH reduction of the tetrazole (XI) after heating under reflux in ether solution for 10 hours. The reduction product was identical with the compound IX previously obtained.

Further elution gave a complex mixture which was rechromatographed on a silica gel column eluting with 1% methanol in chloroform. An additional amount of benzimidazole (IX) (17% yield) was first eluted followed by crude *N*-(2-aminophenyl)-2-pyrrolidone (X) (8% yield). Recrystallization gave pure X, m.p. 103-104°, identical in all respects to an authentic sample (16) by mixed m.p., ir and nmr spectra.

*N*-(2-Aminophenyl)pyrrolidine.

This compound was obtained by LAH reduction of the pyrrolidone (X) after heating under reflux in ether solution for 10 hours. The crude reaction product purified by vacuum distillation (b.p. 70-75° at 0.001 mm Hg) was identical with an authentic sample (24) (ir and nmr spectra).

The residue from the mother liquor of crystallization of X was purified by preparative tlc (silica gel, 1% methanol in chloroform) yielding pure 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazocin-6-one (XII) (2% yield); mass spectrum: *m/e* (1%), 176 (40.7) $M^+$ , 159 (5.5), 147 (100), 146 (49.9), 133 (22.2), 132 (33.3), 130 (20.3), 121 (5.5), 120 (18.5), 119 (42.5), 118 (31.4), 117 (14.8), 106 (12.9), 105 (46.2), 104 (31.4), 103 (5.5), 93 (12.9), 92 (44.4), 91 (29.6), 90 (18.5), 78 (24.0), 77 (49.9), 76 (14.8), 75 (9.2), 74 (11.1), 65 (25.9), 64 (24.0), 63 (22.2), 56 (12.9), 51 (27.7), 50 (14.8), 44 (7.4), 43 (12.9), 41 (12.9), 39 (24.0), 30 (25.9), 28 (25.9), 27 (11.1), 18 (3.7).

*Anal.* Calcd. for  $C_{10}H_{12}N_2O$ : C, 68.16; H, 6.86; N, 15.90. Found: C, 67.98; H, 6.78; N, 15.81.

Schmidt Reaction on *N*-Tosyl-1,2,3,4-tetrahydro-1-benzazepin-5-one (VIIIa) (12b).

The crude reaction product was purified in the same way as described in the last reaction. The products and relative yields were as follows: benzimidazole (IX) (58%); tetrazole (XI) (5%); pyrrolidone (X) (4%); benzodiazocinone (XII) (2%). In addition to the above compounds 7-tosyl-4,5,6,7-tetrahydro-tetrazolo[5,1-*e*]-1,6-benzodiazocine (XIa) was eluted from the column in a mixture with tetrazole (XI). Preparative tlc gave pure XIa which was further purified by recrystallization (2% yield).

*Anal.* Calcd. for  $C_{17}H_{17}N_5O_2S$ : C, 57.46; H, 4.82; N, 19.71. Found: C, 57.23; H, 4.79; N, 19.84.

## Lithium Aluminum Hydride Reduction of Tetrazole (XIa).

The benzimidazole (IX) was obtained by LAH reduction of tetrazole (XIa), in a similar fashion to that described for the LAH reduction of tetrazole (XI).

## 1,2,3,4,5,6-Hexahydro-1-benzazocin-6-ol.

3,4-Dihydro-1*H*-1-benzazocin-2,6(5*H*)dione (25) (0.05 mole) was reduced in an ethereal solution of LAH (0.5 mole) by refluxing for 24 hours. The crude residue obtained after the usual procedure was crystallized several times to obtain pure benzazocinol (65% yield) m.p. 87-89°. This product was identical (m.p., ir and nmr data) with an authentic sample obtained *via* an

independent method (26).

*N*-Acetyl derivative (XVI) was obtained by treatment of the above benzazocinol with acetic anhydride for 6 hours at room temperature followed by alkaline hydrolysis (15% aqueous potassium hydroxide) for 12 hours of the intermediate diacetyl derivative. After recrystallization from benzene, pure XVI m.p. 152-154°; ir (nujol):  $\nu$  OH 3440,  $\nu$  CO 1653  $cm^{-1}$ ; nmr aromatic 7.93-6.90 m (4H); 4.83-2.67 m (3H: -CH-OH, CH<sub>2</sub>-N-); 3.77 b (OH); 1.80 s (-COCH<sub>3</sub>); 1.53 m (6H: -CHOH-(CH<sub>2</sub>)<sub>3</sub>-C-), was obtained.

*Anal.* Calcd. for  $C_{13}H_{17}NO_2$ : C, 71.20; H, 7.82; N, 6.39. Found: C, 71.32; H, 7.75; N, 6.26.

The *N*-Tosyl derivative was obtained by treatment of the above benzazocinol with tosyl chloride in pyridine for 3 hours at room temperature. The mixture was poured into water to give the crude *N*-tosyl derivative. This solid derivative was purified by recrystallization from ethanol and was identical (m.p. 166-168° and ir data) with an authentic sample obtained by an independent method (26).

1-Acetyl-2,3,4,5-Tetrahydro-(1*H*)-1-benzazocin-6-one (XIIIb).

Chromic acid anhydride (2 g.) was slowly added with stirring to anhydrous pyridine (20 ml.) at 10-15°. After a further 30 minutes, a solution of the *N*-acetyl derivative (XVI) (2 g.) in pyridine was added. The oxidation was complete after 6-7 hours at room temperature. The reaction mixture was diluted with chloroform (100 ml.) and then filtered. The chloroform solution was washed with dilute hydrochloric acid, water and then dried (calcium chloride) and evaporated. The crude product was purified by silica gel column chromatography eluting with chloroform. Pure XIIIb was obtained (64%) by further recrystallization.

*Anal.* Calcd. for  $C_{13}H_{15}NO_2$ : C, 71.86; H, 6.96; N, 6.45. Found: C, 71.80; H, 6.85; N, 6.30.

1-Tosyl-2,3,4,5-tetrahydro-1*H*-1-benzazocin-6-one (XIIIa).

This compound was obtained by a similar oxidation as described above starting from the *N*-tosyl derivative of benzazocinol. Pure crystals from methanol were identical (m.p. 144-145° and ir data) to an authentic sample obtained by an independent way (26).

2,3,4,5-Tetrahydro-1*H*-1-benzazocin-6-one (XIII).

The foregoing *N*-acetyl derivative (XIIIb) (1.5 g.) was refluxed with an 8% aqueous sodium hydroxide solution (20 ml.) for 4 hours and cooled. The mixture was extracted with ether. The combined extracts were dried (sodium sulfate) and evaporated to give a crude residue which was chromatographed on a silica gel column. The column was eluted with 1:1 ethyl acetate-hexane to give practically pure XIII, further purified by recrystallization.

Schmidt Reaction on 2,3,4,5-Tetrahydro-1*H*-1-benzazocin-6-one (XIII).

The crude reaction products obtained from the Schmidt reaction on benzazocinone (XIII), its *N*-tosyl (XIIIa) and *N*-acetyl (XIIIb) derivatives showed close similarity in composition and are described in a unique way. The solid residue, by repeated recrystallization, gave pure 1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole (XIV), m.p. 100-101° (yield ca. 30%), identical in all respects to an authentic sample (17). The residue from the mother liquor of crystallization of the benzimidazole (XIV) was chromatographed on a silica gel column eluting with ethyl acetate, 4,5,6,7-Tetrahydro-8*H*-tetrazolo[5,1-*f*]-1,7-benzodiazocine (XV) (23% yield) was first eluted from the column and was purified by recrystallization.

*Anal.* Calcd. for  $C_{11}H_{13}N_5$ : C, 61.37; H, 6.09; N, 32.54. Found: C, 61.19; H, 6.04; N, 32.51.

Lithium Aluminum Hydride Reduction of Tetrazole (XV).

The benzimidazole (XIV) in a pure form was obtained by LAH reduction by refluxing an ethereal solution of the tetrazole (XV) for 12 hours.

Further elution of the column gave an additional amount of the benzimidazole (XIV) (ca. 25% yield) practically pure.

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