1,2,3,5-Tetrahydro-4*H*-1,5-benzodiazepin-4-ones and 1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-5-ones from the Reaction of Hydrazoic Acid on 1,2,3,4-Tetrahydroquinolin-4-ones.

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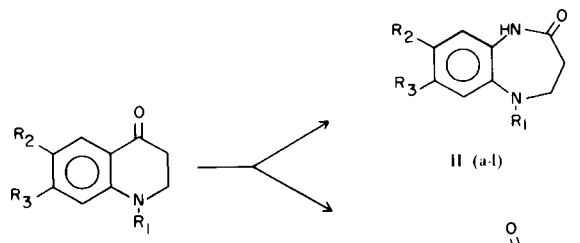
Received December 12, 1970

The Schmidt reaction on 1,2,3,4-tetrahydroquinolin-4-ones (I) gave 1,2,3,5-tetrahydro-1,5-benzodiazepin-4-ones (II) and 1,2,3,4-tetrahydro-1,4-benzodiazepin-5-ones (III). The ratio of II and III is dependent upon substituents present on the nitrogen ring atom of the quinolinones.

Recently Wünsch, Stahnke and Gomoll (1) reported the preparation of 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (IIIa) in 31% yield *via* the Schmidt reaction on 1,2,3,4-tetrahydroquinolin-4-one (Ia). This prompted us to report the results of similar work on the synthesis of potential antidepressives. The same reaction in our hands gave compound IIIa in 70% yield together with 1,2,3,5-tetrahydro-4*H*-1,5-benzodiazepin-4-one (IIa) in 18% yield. The latter had a melting point (2,3) and NMR data (4) identical to an independently prepared sample.

The Schmidt reaction on tetrahydroquinolin-4-ones was reported for the first time in 1958 by Ittyerah and Mann (5), who used 1-methyl- and 1-phenyl-1,2,3,4-tetrahydroquinolin-4-one (Ib and Ic). They assigned the structure as 1-methyl-1,2,3,5-tetrahydro-4*H*-1,5-benzodiazepin-4-one (IIb) and 1-phenyl-1,2,3,5-tetrahydro-4*H*-1,5-benzodiazepin-4-one (IIc), respectively to each individual product isolated in each reaction.



I (a-l)

II (a-l)

III (a-l)

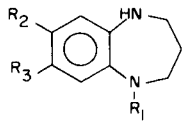
	R_1	R_2	R_3
(a)	H	H	H
(b)	Me	H	H
(c)	Ph	H	H
(d)	Ac	H	H
(e)	H	H	OMe
(f)	Me	H	OMe
(g)	Ac	H	OMe
(h)	H	Cl	H
(i)	Me	Cl	H
(l)	Ac	Cl	H

We repeated the reaction under the same conditions as Ittyerah and Mann using the quinolinone Ib and isolated 1-methyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (IIIb) (*ca.* 60% yield) and 1-methyl-1,2,3,5-tetrahydro-4*H*-1,5-benzodiazepin-4-one (IIb) (*ca.* 20% yield). Similarly in the reaction on the quinolinone Ic, 1-phenyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (IIIc) (*ca.* 85% yield) together with 1-phenyl-1,2,3,5-tetrahydro-4*H*-1,5-benzodiazepin-4-one (IIc) (*ca.* 5% yield) were identified. The benzodiazepinones IIIb and IIIc gave the same melting point as the compounds identified previously (5) as IIb and IIc respectively. The structure of the benzodiazepinone IIIb was confirmed by comparison with an authentic sample synthesized by a different route (6). The assignment of the relative structures of the isomers II, IIIb and II, IIIc was also based on chemical and spectroscopic evidence. Lithium aluminum hydride reduction of the 1,4-benzodiazepinones IIIb and IIIc gave the 1,4-benzodiazepines Vb and Vc which show a singlet in the NMR spectrum (*ca.* 3.85 δ) assigned to the benzylic-methylene group. However this signal was absent in the NMR spectrum of 1-methyl-1,2,3,4-tetrahydro-5*H*-1,5-benzodiazepine (IVb) prepared from the lithium aluminum hydride reduction of 1,5-benzodiazepinone IIb. The NMR spectrum of IVb showed a multiplet (*ca.* 1.85 δ), assigned to the C-3 methylene group, which was identical to that observed for the benzodiazepine IVa (3,13) (Table IV). In addition the above tetrahydrobenzodiazepine Vb showed physico-chemical properties identical to those of the 1-methyl 1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepine described by Santilli and Osdene (6).

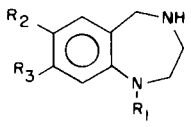
TABLE I

Migratory Tendencies in the Schmidt Reaction of Tetrahydroquinolin-4-ones

	1,2,3,4-Tetrahydroquinolin-4-ones				Isomer ratio	
	R_1	R_2	R_3	Yield %	% aryl migration	% alkyl migration
Ia	H	H	H	88	20	80
Ib	Me	H	H	82	25	75
Ic	Ph	H	H	90	5	95
Id	Ac	H	H	85	95	5
Ie	H	H	OMe	95	30	70
If	Me	H	OMe	92	35	65
Ig	Ac	H	OMe	90	90	10
Ih	H	Cl	H	92	35	65
Ii	Me	Cl	H	91	25	75
Il	Ac	Cl	H	80	90	10



IV

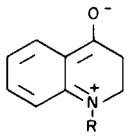


V

The proposed structures for isomers II and III were differentiated based upon a comparison of the NMR data. The NMR of IIIb and IIIc showed a split doublet at low field (7.6 δ, $J_{2,5}$ cps, J_9 cps) integrating for one proton which was assigned to the aromatic proton in position 6 (*i.e. ortho* to carbonyl); this was absent in the spectra of the corresponding benzodiazepinones IIb and IIc. Another difference was that, while the two methylene groups of the benzodiazepinone IIb have different chemical shifts, the corresponding methylene groups of IIIb gave rise to an unresolved multiplet which became a singlet after addition of deuterium oxide; this was also observed by Santilli and Osdene (6).

The formation of isomer III as the major product of the reaction agrees with previous work on the Schmidt reaction for chromanones (4,7) and flavanones (8). More generally, it has been shown that in the Schmidt reaction on benzocycloalkanones with a strong electron-donating group *ortho* or *para* to the carbonyl, the alkyl migration becomes enhanced and in some cases is equivalent to aryl migration (9). These studies have been extended recently by Wünsch *et al.*, to some 1-thio-4-chromanones (10).

The fact that certain tetrahydroquinolin-4-ones gave a major percentage of the benzodiazepinone compound due to alkyl migration compared to the percentage of the isomeric compound due to aryl migration, can be explained by postulating a resonance structure of the following type which would hinder aryl migration.



(A)

In a preliminary study of the effect of substituents on both the aromatic ring and on the nitrogen atom of the tetrahydroquinolin-4-ones, we have extended the Schmidt reaction to other 1,2,3,4-tetrahydroquinolin-4-ones which are reported in Table I. From these results it can be concluded that the ratio of the II and III isomers obtained from the unsubstituted quinolinone Ia is not greatly influenced when either electron-donating or withdrawing substituents are present on the aromatic ring. This is in agreement with observations (4) on analogous substituted 4-chromanones. The ratio is also not influenced by substitution of a methyl group on the ring nitrogen but is almost completely displaced towards the isomer III (alkyl migration) by substitution of a phenyl group (IIIc $\gg$ IIc). The phenyl group is twisted out of plane and aids the formation of resonance structure A by the +I effect. Displacement towards the isomer II occurs when the

TABLE II

1,2,3,5-Tetrahydro-4*H*-1,5-benzodiazepin-4-ones (II)

	m.p. °C (Recryst. Solv.)	NMR (δ) -NH-CO-	-NH-	Aromat.	$-CH_2-NR_1-$	$-CH_2-CO-$	$-CH_3$	IR cm^{-1} ν NH	ν CO
IIa (2,3)	141-142 (benzene-hexane)	8.78	3.50	7.2-6.6 m	3.67 t	2.75 t		3350, 3170	1660 bs
IIb	138-140 (benzene-hexane)	9.10		7.05 m	3.55 t	2.52 t	2.83 s (NMe)	(a) 3100-3000	1683 b
IIc	181.5-182.5 (ethanol)	8.15		7.4-6.6 m	4.02 t	2.63 t		3360, 3150	1670 s
IId	159-161 (ethyl acetate-hexane)	9.33		7.27 m	4.90 b 3.50 b	2.63 m	1.85 s (NAc)	3330, 3150	1640-1680 bs
IIe	158-159 (ethyl acetate)	(b) 5.93	4.87	7.35-6.4 m	3.70 t	2.78 t	3.65 s (OMe)	(a) 3270, 3100	1655 bs
IIf	150-152 (ethyl acetate-hexane)	8.50		7.10-6.35 m	3.50 t	2.48 t	2.80 s (NMe) 3.80 s (OMe)	3320, 3120	1660 bs
IIg	219-221 (ethyl-acetate-hexane)	9.20		7.30-6.6 m	4.90 b 3.50 b	2.60 m	1.88 s (NAc) 3.83 s (OMe)	3350, 3160	1670 bs
IIh (12)	183-184 (ethyl acetate-hexane)	(b) 10.55	6.10	7.40-6.8 m	3.63 m (c)	2.80 t		3320, 3150	1665 bs
IIi	140-142 (ethyl acetate-hexane)	8.90		7.3-6.8 m	3.53 t	2.50 t	2.80 s (NMe)	3350, 3170	1672 bs
III	240-241 (ethanol)	(d) 9.80		7.20 bs	4.75 b 3.40 b	2.57 m	1.77 s (NAc)	(a) 3120-3000	1640, 1680 bs

(a) Nujol. (b) Solvent, perdeuteriopyridine. (c) Triplet on addition of deuterium oxide. (d) Solvent, deuteriochloroform-hexadeuteriodimethylsulphoxide.

TABLE III

1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepin-5-ones (III)

	m.p. °C (Recryst. Solv.)	NMR (δ) -NH-CO-	-NH-	Aromat.	-CH_2-N-	-CH_3	IR cm^{-1} ν NH	ν CO
IIIa (1)	155-156 (AcOEt-hexane)	7.63	4.40	7.93 dd (a) (H-6); 7.20 dt (a) (H-8); 6.9-6.4 m	3.53 m (b) (4H)		(c) 3580, 3380	1670 bs
IIIb (6)	169-170 (benzene)	8.43		7.67 dd (a) (H-6); 7.37 dt (a) (H-8); 7.1-6.7 m	3.30 m (b) (4H)	2.83 s (NMe)	(c) 3220	1655 bs
IIIc	226-228 (ethanol)	(d) 8.05		7.65 dd (a) (H-6); 7.50-6.50 m	3.67 t (2H) 3.40 m (e) (2H)		3350, 3130	1655 bs
IIId	174-176 (ethyl acetate)	7.60		8.00-7.10 m	4.80 b (1H) 3.40 b (1H) 3.40 m (2H)	1.90 s (NAc)	3350, 3200	1655 bs
IIIe	192-194 (ethyl acetate)	(f) 8.70	6.90	8.55 d (g) (H-6) 6.50 m	3.50 m (b) (4H)	3.60 s (OMe)	(c) 3320, 3170, 3080	1630 bs
IIIf	161-162 (ethyl acetate)	8.00		7.70 d (g) (H-6) 6.60-6.30 m	3.30 m (b) (4H)	2.85 s (NMe) 3.82 s (OMe)	3380, 3230, 3150	1645 bs
IIIg	205-206 (ethyl acetate)	7.00		7.72 d (g) (H-6); 6.95 dd (a) (H-7); 6.67 d (h) (H-9)	4.67 b (1H) 3.30 b (1H) 3.35 m (2H)	1.83 s (NAc) 3.83 s (OMe)	3380, 3270, 3180	1655 bs
IIIh	150-151 (ethanol)	(f) 9.05	7.10	8.50 d (h) (H-6); 7.27 dd (a) (H-8); 6.9 d (g) (H-9)	3.50 m (b) (4H)		(c) 3220, 3080	1630 bs
IIIi	186-188 (ethyl acetate)	8.00		7.70 d (h) (H-6); 7.35 dd (a) (H-8); 6.82 d (g) (H-9)	3.37 m (b) (4H)	2.85 s (NMe)	3400, 3170	1655 bs
IIIl	204-206 (ethyl acetate)	7.50		7.75 d (h) (H-6); 7.50 dd (a) (H-8); 7.10 d (g) (H-9)	4.73 b (1H) 3.30 m (1H) 3.35 m (2H)	1.83 s (NAc)	3360, 3180	1660 bs

(a) J = 2.5 cps, J = 8.5 cps. (b) Apparent singlet on addition of deuterium oxide. (c) Nujol. (d) Solvent, deuteriochloroform-hexadeuteriodimethylsulphoxide. (e) Triplet on addition of deuterium oxide. (f) Solvent, perdeuteriopyridine. (g) J = 9 cps. (h) J = 2.5 cps.

TABLE IV

1,2,3,4-Tetrahydro-5*H*-1,5-benzodiazepines (IV) and 1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepines (V)

	b.p. °C/mm Hg (m.p. recryst. solv.)	NMR (δ)						IR cm^{-1}
		-NH-	Aromat.	$-CH_2-N-$	$-C-CH_2-C-$	$-CH_2$-(benzylic)	$-CH_3$	ν NH
IVa (3,13)	(100-102°; pet. eth.)	3.67 b (2H)	6.67 bs	3.05 m (4H)	1.80 m			3300
IVb	125-30/0.005	3.47 b	6.80 m	3.07 m (4H)	1.87 m		2.90 s (NMe)	(a) 3380
IVe	115-20/0.005	3.60 s (2H)	6.8-6.2 m	2.98 m (4H)	1.80 m		3.72 s (OMe)	(a) 3350
Vb (6)	60-70/0.005	1.90 s	7.4-6.7 m	3.00 m (4H)		3.92 s	2.92 s (NMe)	(a) 3250
Vc (a)	115-20/0.05	2.20 bs	7.4-6.4 m	3.72 t (2H)		3.83 s		(a) 3250
				3.08 t (2H)				

(a) Film.

nitrogen is substituted with a strongly electron-attracting substituent such as an acetyl group (IId,g,l ≫ IIId,g,l).

The Schmidt reaction was finally extended to the 1-tosyl-1,2,3,4-tetrahydro-4-quinolinone (Il), but the reaction conditions caused detosylation of the starting material; thus the same ratio between isomer II and III was obtained as in the reaction on the unsubstituted tetrahydroquinolinone Ia.

Tables II, III and IV report the 1,5-benzodiazepinones II, the 1,4-benzodiazepinones III and some of the corresponding lithium aluminum hydride-reduced compounds obtained, with the important spectroscopic data. Structural assignments were made as shown before for benzodiazepinones IIb,c and IIIb,c. Again, NMR evidence was the most useful in distinguishing between isomers II and III.

Finally the *N*-acetyl-1,4-benzodiazepinones IIId,g,l were prepared by acetylation of the corresponding 1,4-benzodiazepinones IIIa,e,h at room temperature, in order to compare them with the same compounds isolated (in very poor yield) in the Schmidt reaction on the *N*-acetylquinolinones Id,g,h.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are 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 chloroform solution unless otherwise stated. Chemical shifts are measured in ppm (δ) with respect to TMS as an internal standard. The peaks assigned to the protons from the -NHCO- and -NH- groups (Tables II, III and IV) disappeared after exchange in deuterium oxide. Thin layer chromatography studies were accomplished using plates of silica gel (Merck GF_{254}).

1,2,3,4-Tetrahydroquinolin-4-ones (I).

The starting tetrahydroquinolinones (Table I) were prepared according to the general method of Atwal *et al.* (14). The respective physico-chemical properties correspond to those reported: 1,2,3,4-tetrahydroquinolin-4-one Ia,b,e,f (14); Ic,h (15); Id (16); Il (17).

The tetrahydroquinolinone Ig, b.p. 128-130°/0.005 mm., was prepared by acetylation of Ie.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.56; H, 5.85; N, 6.25.

The tetrahydroquinolinone Ii was prepared by methylation of Ib with methyl iodide, m.p. 78-80° when crystallized from cyclohexene.

Anal. Calcd. for $C_{10}H_{10}ClNO$: C, 61.34; H, 5.15; N, 7.21. Found: C, 61.59; H, 5.31; N, 6.96.

Schmidt Reaction on 1,2,3,4-Tetrahydroquinolin-4-ones. General Conditions.

Concentrated sulfuric acid (2.5 ml.) was added with cooling and stirring to a solution of the tetrahydroquinolinone I (0.5 g.) in chloroform (5 ml.), then sodium azide (0.5 g.) was added gradually over 30-40 minutes. In general the reaction was complete after about 2 hours at room temperature. The reaction mixture was cooled and then neutralized with an aqueous solution of

TABLE V

Compound	Formula	Elemental Analysis Calcd. C	H	N	Found C	H	N
IIb	$C_{10}H_{12}N_2O$	68.16	6.86	15.90	67.92	6.74	15.92
IIc	$C_{15}H_{14}N_2O$	75.60	5.92	11.76	75.72	5.74	11.90
IIIc	$C_{15}H_{14}N_2O$	75.60	5.92	11.76	75.39	5.90	11.91
IId	$C_{11}H_{12}N_2O_2$	64.69	5.92	13.72	64.44	5.82	13.61
IIId	$C_{11}H_{12}N_2O_2$	64.69	5.92	13.72	64.30	5.89	13.73
IIe	$C_{10}H_{12}N_2O_2$	62.48	6.29	14.58	62.71	6.27	14.81
IIIe	$C_{10}H_{12}N_2O_2$	62.48	6.29	14.58	62.33	6.29	14.62
IIf	$C_{11}H_{14}N_2O_2$	64.06	6.84	13.58	64.14	6.78	13.75
IIIf	$C_{11}H_{14}N_2O_2$	64.06	6.84	13.58	64.17	6.82	13.46
IIg	$C_{12}H_{14}N_2O_3$	61.52	6.02	11.96	61.71	5.89	11.73
IIIg	$C_{12}H_{14}N_2O_3$	61.52	6.02	11.96	61.64	6.14	12.09
IIIh	$C_9H_9ClN_2O$	54.97	4.61	14.25	55.19	4.48	14.18
IIi	$C_{10}H_{11}ClN_2O$	57.01	5.26	13.30	57.06	5.29	13.59
IIIi	$C_{10}H_{11}ClN_2O$	57.01	5.26	13.30	56.87	5.28	13.21
III	$C_{11}H_{11}ClN_2O_2$	55.35	4.64	11.74	55.52	4.60	11.70
IIII	$C_{11}H_{11}ClN_2O_2$	55.35	4.64	11.74	55.20	4.62	11.51
IVb	$C_{10}H_{14}N_2$	74.03	8.70	17.27	74.28	8.65	17.04
IVc	$C_{10}H_{14}N_2O$	67.38	7.92	8.98	67.56	7.70	8.78

sodium carbonate and finally extracted exhaustively with ethyl acetate. The combined extracts were dried over sodium sulfate. The crude residue was heated with ethyl acetate and in general the least soluble benzodiazepinone III separated. The ethyl acetate filtrate was then chromatographed on a silica gel column. On elution with ethyl acetate gradually enriching with ethanol, first the benzodiazepinone II was obtained, and then practically pure III. In the reactions on tetrahydroquinolinones Id,g, and l, the residue from the reaction gave, after recrystallization from ethyl acetate, practically pure benzodiazepinone II (IId,g,l). The ethyl acetate filtrate contains a small quantity of III (IIId,g,l) (Tables II and III).

1,2,3,4-Tetrahydro-5*H*-1,5-benzodiazepine (IV) and 1,2,3,4-Tetrahydro-5*H*-1,4-benzodiazepine (V).

Compounds IV and V (Table IV) were obtained by lithium aluminum hydride reduction of the benzodiazepinones II and III, respectively, after heating under reflux in ether solution for 10-12 hours.

Acknowldegment.

We thank Miss G. Camarda for technical assistance and Dr. M. Marzadro for microanalysis.

REFERENCES

(1) K. H. Wünsch, K. H. Stahnke and P. Gomoll, *Z. Chem.*, 10, 219 (1970).

(2) B. Bachman and L. V. Heisey, *J. Am. Chem. Soc.*, 71, 1985 (1949).

(3) J. Davoll, *J. Chem. Soc.*, 308 (1960).

(4) G. S. Sidhu, G. Thyagarajan and U. T. Bhalerao, *ibid.*, (C), 969 (1966).

(5) P. I. Ittyerah and F. G. Mann, *ibid.*, 467 (1958).

(6) A. Santilli and T. S. Osdene, *J. Org. Chem.*, 31, 4268 (1966).

(7a) D. Huckle, I. M. Lockhart and M. Wright, *J. Chem. Soc.*, 1137 (1965); (b) U. T. Bhalerao and G. Thyagarajan, *Can. J. Chem.*, 46, 3367 (1968).

(8) I. M. Lockhart, *Chem. Ind.* (London), 1844 (1968); D. Misiti and V. Rimatori, *Tetrahedron Letters*, 947 (1970).

(9a) T. Ichii, *J. Pharm. Soc.* Japan, 82, 999 (1962); *Chem. Abstr.*, 58, 5666 (1963); (b) D. Evans and I. M. Lockhart, *J. Chem. Soc.*, 4806 (1965); (c) M. Tomita, S. Minami and S. Uyeo, *ibid.*, (C), 183 (1969) and references therein; (d) J. B. Hester Jr., A. D. Rudzik and W. Veldkamp, *J. Med. Chem.*, 13, 827 (1970).

(10) K. H. Wünsch, K. H. Stahnke and A. Ehlers, *Chem. Ber.*, 103, 2302 (1970) and references therein.

(11) W. S. Johnson, E. L. Woroch and B. G. Buell, *J. Am. Chem. Soc.*, 71, 1901 (1949).

(12) R. M. Acheson and W. R. Tully, *J. Chem. Soc.*, (C), 1117 (1970).

(13) O. Hinsberg and A. Strupler, *Ann. Chem.*, 287, 220 (1895); H. Stetter, *Chem. Ber.*, 86, 197 (1953); O. E. Fancher and G. Nichols, U. S. Patent 2,899,359; *Chem. Abstr.*, 54, 598 (1960); T. Ichii, *J. Pharm. Soc.* Japan, 82, 992 (1962), *Chem. Abstr.*, 58, 5666 (1963).

(14) M. S. Atwal, L. Bauer, S. N. Dixit, J. E. Gearien and R. W. Morris, *J. Med. Chem.*, 8, 566 (1965) and references therein.

(15) C. D. Hurd and S. Hayao, *J. Am. Chem. Soc.*, 76, 5065 (1954).

(16) R. F. Collins, *J. Chem. Soc.*, 2053 (1960).

(17) A. F. Bekli, *Doklady Akad. Nauk S.S.S.R.*, 101, 679 (1955); *Chem. Abstr.*, 50, 3441[a] (1956).