Substituted 1,3-Dihydro-4*H*-furo[3,4-*d*]-1,3-benzodiazepin-3-ones: Synthesis and Scope of the Method

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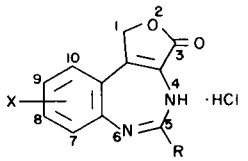
The preparation of a series of 1,3-dihydro-4*H*-furo[3,4-*d*]-1,3-benzodiazepin-3-ones has been studied. This study and the compounds prepared tend to illustrate that the limiting factor in the scope of the synthetic method is similar to that noted generally in the Fisher indole synthesis. The lactone ring is relatively stable under a variety of conditions, and is believed to lend ease of formation to the ring system studied.

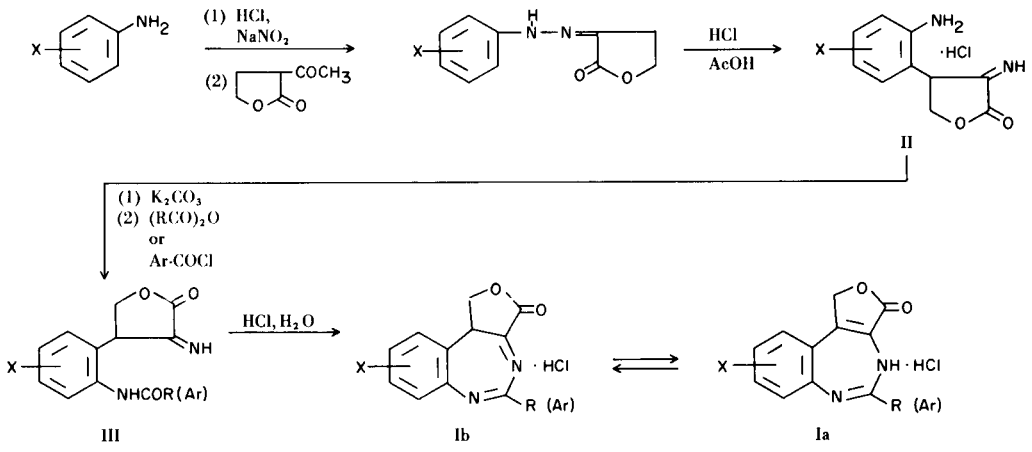
Although the literature is quite extensive regarding the synthesis and importance of 1,2-, 1,4-, and 1,5-benzodiazepines (4-7) as chemical and, particularly, medicinal agents, there is an unusual lack of information concerning similar systems having nitrogen atoms in different positions in the seven membered ring. A report by Plieninger and Nogradi (8) in 1955 was the only report of a compound of general structure I, which might be described as a derived 4*H*-1,3-benzodiazepine. The authors presented the structure and synthesis of this compound which was obtained during a reaction that failed to yield an anticipated oxymethyl indole carboxylic acid *via* the Fisher synthesis. After Plieninger's initial report (8), no further work was published in this area until deStevens (9) reported on tetrahydro-1,3-benzodiazepines and Rodriquez, *et al.* (10) published their work on dihydro-3*H*-1,3-benzodiazepines.



(I)

The present study was undertaken in order to broaden the scope of knowledge concerning the synthesis of derived 1,3-benzodiazepines with variable substitution. The synthetic approach utilized in this study follows Plieninger's original route with some slight alterations. The general method of preparation is presented in Scheme I. It is presumed that in order to maintain maximum stability, structure Ia is the preferred form of the compound and of subsequent derivatives.

SCHEME I



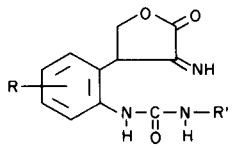
It was noted that when R = methyl, ethyl, or propyl, in Scheme I, the anhydride reaction giving III proceeded quite well after II was first converted to its free base. Alternately, when R = methyl, the amine hydrochloride could be used as such, the acylation being carried out with acetic anhydride in aqueous solution. The hydrochloric acid liberated *in situ* during the reaction was sufficient to initiate the ring closure which then could be carried to completion by the addition of dilute aqueous hydrochloric acid. As would be expected sterically, as R increases in size, the rate of formation of I becomes slower. When R = phenyl, the ring closure reaction occurred very slowly, requiring the use of external heat or long periods of shaking.

The yield of products in all cases was fair to good including those reactions in which *m*-anisidine, *p*-anisidine and *p*-toluidine were used as starting materials for the preparation of the intermediate hydrazones. However, as might be expected from the mechanism of the Fisher indole synthesis, electronegative substituents in the aromatic ring prevented the second stage rearrangement shown in Scheme I. Such a case was noted when attempting to rearrange the hydrazones obtained with *meta* or *para* chloro- and *meta* or *para*-nitroanilines. In each case, practically quantitative recovery of the starting hydrazones resulted. In the same regard, it was interestingly noted that although *o*-toluidine reacted in good yield to form the hydrazone, and also rearranged in what appeared to be a good yield, based upon the amount of recoverable hydrazone, the 3-imino-4-(2-amino-3-tolyl)-tetrahydro-2-furanone presumably formed could not be purified. Attempts at acylating the non-purified material failed and consequently the exploration of this compound in the synthetic series was abandoned.

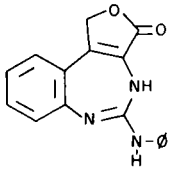
During the course of the experiments concerned with the rearrangement of the hydrazones, it was found that one of the most critical points in the rearrangement was the rate of introduction of anhydrous hydrogen chloride. For maximum yield, ease of isolation and greatest purity of compounds of general structure II·hydrochloride, it was found that introduction of hydrogen chloride was best carried out at a rate that would produce a temperature of 70-85° in about 20 minutes without external heat. It was also noted that the hydrazones should be completely free of solvents, especially water, in order to facilitate isolation and purification of the resulting substituted 3-imino-4-(2-aminophenyl)-tetrahydro-2-furanone hydrochlorides. This was best accomplished by filtering the respective hydrazone from a slurry in acetic acid after stirring at 60° for 0.5 hour.

In all derivatives tested, little or no difficulty was encountered in preparing the substituted acyl derivatives (III) from the imino-amines, except as noted previously for the reaction utilizing *o*-toluidine as the starting product. The limiting factor in the isolation of the acyl derivatives (general structure III) was the use of appropriate solvent conditions such that the product crystallized from the reaction mixture. The analytical data for the synthesized acylated arylaminofuranones appears in Table III. As noted for several compounds in the table, infrared absorptions for the acyl derivatives occurred at the expected frequencies for the C=O with some minor shift in the anticipated direction depending upon the influence of adjacent aryl *vs.* alkyl substituents. Also of note is the relatively non-deviating position of the lactone absorption band at 1748-1752 cm^{-1}.

During the course of testing the reactivity of the Plieninger-Fisher intermediate, we found that the known amine-isocyanate reaction proceeded with relative ease resulting in the formation of IV and V by reaction with phenylisocyanate and butylisocyanate. However, efforts to promote ring closure of V failed in hydrochloric acid (cold and warm; 2*N* to 8*N*), by heating in polyphosphoric acid (PPA) (150-180°) and by heating in Dowtherm (up to 220°). A reaction, presumed to be ring closure, did occur when IV was heated in PPA. The analysis obtained was in fair agreement for VI·phosphate.



IV: R=H, R'=Ph
V: R=H, R'=Bu



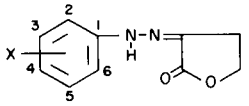
VI

To further establish that IV did indeed ring close to VI, the phosphate salt was converted to its free base and crystallized as its hydrochloride·hydrate. This was dried extensively to give VI·hydrochloride as greenish-yellow flakes. The yield of end product was relatively poor because of extensive decomposition of the diazepine in the 10% sodium hydroxide required for free base formation from VI·phosphate.

Cyclization to the benzo-1,3-diazepine structure (I) occurred readily among the cases we studied where R (or Ar) was an unbranched alkyl or an unsubstituted phenyl group. Cyclization failed when R (or Ar) was *p*-NO_2-C_6H_4-, *m*-NO_2-C_6H_4-, C_2H_5O-$\overset{O}{\overset{\|}{C}}$-, $(CH_3)_3C$-, $C_6H_5CH_2$-, $CH_3OCH_2CH_2$- and C_4H_9NH-. The reason for these observations is not readily apparent. It may be that the extreme insolubility of some of these compounds (such as the nitrophenyls) in the acidic solution used for cyclization was the limiting factor. In addition, in certain of the substituents given above, a potential positive charge on the acyl carbon is not possible. When Ar = *p*-$NO_2C_6H_4$-,

TABLE I

Substituted 3-Aryl Tetrahydro-2-furanone Hydrazones

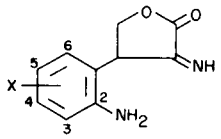


Formula	X	M.p. °C (dec.)	Yield (%)	Analysis Calculated C	H	N	Found C	H	N
$C_{10}H_{10}N_2O_2$	H (a)	223.5-224.5	96.8	63.15	5.70	14.73	63.10	5.62	14.78
$C_{11}H_{12}N_2O_2$	2-Me	200.6-201.8	98	64.68	5.93	13.69	64.40	5.79	14.10
$C_{11}H_{12}N_2O_2$	4-Me	247.5-249	91.4	64.68	5.93	13.69	64.63	5.98	13.79
$C_{11}H_{12}N_2O_3$	3-OMe	216-218	84.3	60.00	5.49	12.72	59.55	5.29	12.26
$C_{11}H_{12}N_2O_3$	4-OMe	240.5-242	94.2	60.00	5.49	12.72	59.76	5.38	12.61
$C_{10}H_9ClN_2O_2$	2-Cl	197.3-200	46	53.47	4.04	12.46	53.61	4.02	12.00
$C_{10}H_9ClN_2O_2$	4-Cl	211.3-214.1	78	53.47	4.04	12.46	53.12	3.96	11.98
$C_{10}H_9N_3O_4$	2-NO_2	201.3-205	51	51.07	3.86	17.86	51.51	3.59	17.44
$C_{10}H_9N_3O_4$	4-NO_2	228-231	70	51.07	3.86	17.86	51.44	3.66	17.38

(a) Duffin (13) reports 228° as the m.p.

TABLE II

Substituted 3-Imino-4-(2-aminophenyl)-tetrahydro-2-furanone

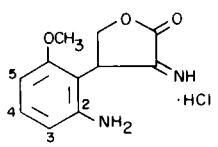


Formula	X	M.p. °C	Yield (%)	Analysis Calculated C	H	N	Found C	H	N
$C_{10}H_{10}N_2O_2$·HCl	H (a)	179-180.3 (c)	93.5	52.98	4.98	12.35	52.56	4.88	12.30
$C_{10}H_{10}N_2O_2$	H (a,b)	98-99.5	87.2	63.15	5.30	14.72	63.09	5.26	14.95
$C_{11}H_{12}N_2O_2$·HCl	3-CH_3	214-217.5	61.4	54.89	5.44	11.63	54.51	5.21	12.04
$C_{11}H_{12}N_2O_2$·HCl	5-CH_3	190-191 (c)	89.2	54.89	5.44	11.63	54.95	5.52	11.69
$C_{11}H_{12}N_2O_2$	5-CH_3	129.5-131	98.1	64.70	5.92	13.71	64.62	5.88	13.51
$C_{11}H_{12}N_2O_3$	4-OCH_3	----	---	----	---	----	----	---	----
$C_{11}H_{12}N_2O_3$	4-OCH_3	156-158	41.5 (d)	60.00	5.49	12.72	59.92	5.53	12.72
$C_{11}H_{12}N_2O_3$·HCl	5-OCH_3	177.3-179.3 (c)	83.8	51.55	5.11	10.91	51.31	5.04	11.33
$C_{11}H_{12}N_2O_3$	5-OCH_3	102.7-103.9	73	60.00	5.49	12.72	59.71	5.40	12.40

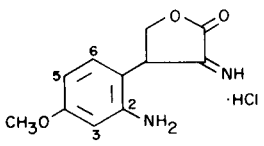
(a) Plieninger (14) reports a m.p. of 184° for the hydrochloride and 86° for the free base. (b) Owellen *et al.*, (11) reports a m.p. of 99-101° for the free base. (c) With decomposition as a red melt. (d) Yield based upon starting hydrazone; hydrochloride salt not isolated.

an alternative ring closure in the presence of hydrochloric acid solutions of stannous and ferrous ions was attempted with the possibility of concurrent reduction of the -NO_2 to -NH_2. In both cases, a stable yellow solid was isolated which unfortunately did not analyze well for any suspected probable compound.

It should be noted that rearrangement of the hydrazone obtained from the reaction of *m*-$CH_3OC_6H_4NH_2$ with nitrous acid and 2-acetylbutyrolactone, could result in either of the 2 compounds (VII or VIII). During the

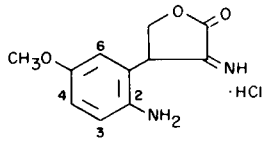


VII



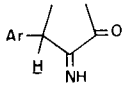
VIII

course of our investigation, it was shown that the free base of the amine·hydrochloride isolated was a pure compound and not a mixture. Only one spot was obtained for the free base and its *N*-acetyl derivative by TLC in two different solvent systems (System I: acetone, chloroform, acetic acid, *n*-butanol (60:30:20:20); R_f's 0.83 and 0.93, respectively. System II: acetone, ethyl acetate, benzene, acetic acid (7.5:60:15:37.5); R_f's 0.68 and 0.77, respectively). Since an unequivocal synthesis of either derivative failed, an NMR analysis of the aromatic protons was undertaken, relative to the pattern known to be produced by IX, which was unequivocal in its structure *via* the reported rearrangement of the hydrazone of *p*-$CH_3OC_6H_4NH_2$ formed with nitrous acid and 2-acetylbutyrolactone.

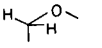


IX

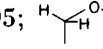
The NMR spectrum of IX (Figure 1) obtained in deuterioacetone clearly shows five sets of different absorptions: relative to tetramethylsilane, CH_3O-, δ 3.86;



, δ 515;



, δ 5.25; Ar proton at C-6, δ 6.81; and at C-3 and 4 a complex multiplet centered at δ 7.0 typical of nearly equivalent aromatics showing the *m*- and *p*- J's to C-6 of 4 and 1.5 cps, respectively. Comparatively, the NMR spectrum of VIII (Figure 2) shows the CH_3O- at δ 3.95;



at δ 5.16; Ar proton at C-3 at δ 7.45, part of an AB pair (J = 8.5 cps), with the second part centered at 6.68, assignable to the C-5 proton; the total aromatic absorption is identifiable as an ABM type. It should be noted that Owellen et al. (11) reports the delta protons of the butyrolactone ring in the unsubstituted Plieninger intermediate as having an NMR absorption at τ 5.18 ppm in deuteriochloroform which would correspond to 4.82 on the δ scale. Compared to IX, this deviation is most likely the effect of solvent. Additionally, the NMR of IX points to the presence of an α-imino structure due to the absorption at δ 5.15 whereas the data of Owellen (11) is in agreement with an α-amino form. Interestingly, the NMR of VIII (Figure 2) and that of the *N*-acetyl derivative of IX in deuterated dimethylsulfoxide do not show an absorption attributable to an

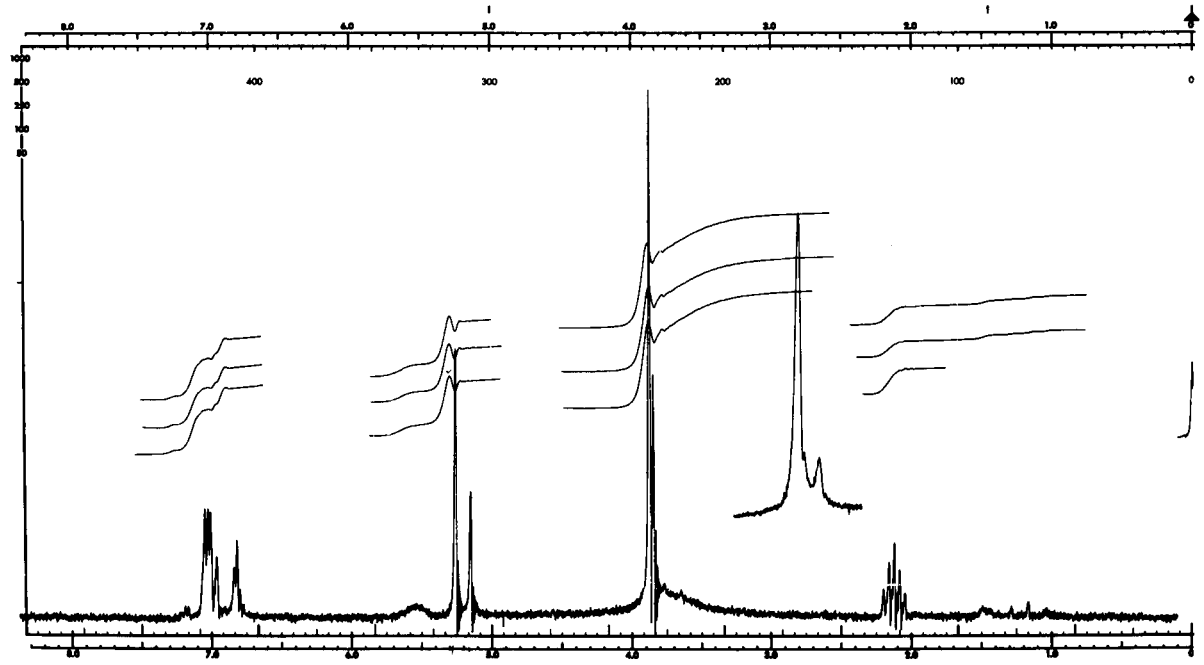
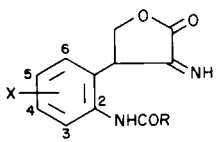


Figure 1. 60 MHz NMR Spectrum of 3-Imino-4-(2-amino-4-anisyl)tetrahydro-2-furanone Hydrochloride in Deuterioacetone. Insert scan; Sweep Offset 190 MHz, Sweep Width 100 Hz.

TABLE III

3-Imino-4-(2-acylaminophenyl)-tetrahydro-2-furanones

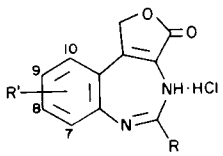


Formula	X	R	M.p. °C	Yield (%)	Analysis Calculated C	H	N	Found C	H	N	ν (cm⁻¹) C=O	Lactone	Reaction solvent
$C_{17}H_{15}N_3O_3$	H	-NHC_6H_5 (a)	193.5-194.2	55.6	66.02	4.88	13.58	65.89	4.70	13.66	1695	1749	CH_3CN
$C_{15}H_{14}N_3O_3$	H	-NHC_4H_9-n (a)	136.4-138	50.8	62.27	6.62	14.52	62.68	6.50	14.11	1705	1752	Hot CH_3CN
$C_{12}H_{12}N_2O_3$	H	CH_3 (b)	191-193 (c)	73.5	62.06	5.21	12.06	62.48	5.09	12.35	1670	1752	H_2O
$C_{13}H_{14}N_2O_3$	H	C_2H_5	189-190.4 (c)	63.8	63.40	5.73	11.38	63.31	5.70	11.18	1673	1748	C_5H_5N
$C_{14}H_{16}N_2O_3$	H	C_3H_7	140-142.8	60.4	64.60	6.20	10.76	64.52	6.18	10.50	1670	1750	C_5H_5N
$C_{17}H_{14}N_2O_3$	H	C_6H_5	172.5-174	78.1	69.38	4.79	9.51	69.60	4.71	9.15	1656	1750	5 vols. C_5H_5N + 2 eq. PhCOCl
$C_{17}H_{13}N_3O_5$	H	-$C_6H_4NO_2$-*p*	174.5-176 (d)	44.5	60.18	3.86	12.38	60.63	3.77	12.55	1675	1751	C_6H_6:C_5H_5N (5:1)
$C_{15}H_{18}N_2O_3$	H	-$C(CH_3)_3$	148.2-150.6	84.3	65.68	6.61	10.21	65.25	6.49	10.66	1680	1751	C_5H_5N
$C_{18}H_{16}N_2O_3$	H	$CH_2C_6H_5$	140-144	33.2	69.89	5.54	9.05	69.42	8.33	8.69	----	----	Dry C_5H_5N at 50°
$C_{14}H_{14}N_2O_5$	H	$CO_2C_2H_5$	161.5-163 (c)	89.7	57.89	4.36	9.65	57.81	4.33	9.41	1690 (f) 1678	1753	C_6H_6, C_5H_5N, anhydrous EtOH (10:0.5:2) (50°)
$C_{17}H_{13}N_3O_5$	H	-$C_6H_4NO_2$-*m*	149-152 (d)	41.2	60.18	3.86	12.38	59.66	3.69	12.01	1660	1753	C_5H_5N
$C_{14}H_{16}N_2O_4$	H	$(CH_2)_2OCH_3$	143-146	39.5	60.82	5.84	10.12	61.42	5.66	10.49	----	----	10:1 C_5H_5N-H_2O
$C_{13}H_{14}N_2O_3$	5-CH_3	CH_3	189-190.5 (e)	88.7	63.40	5.73	11.38	63.29	5.72	11.44	----	----	C_5H_5N (50°)
$C_{14}H_{16}N_2O_3$	5-CH_3	C_2H_5	138-140	48	64.62	6.20	10.74	64.29	6.09	10.51	----	----	5 eq. anhydride
$C_{15}H_{18}N_2O_3$	5-CH_3	C_3H_7	137-138	71.2	65.70	6.62	10.20	66.20	6.85	9.75	----	----	5 eq. anhydride
$C_{13}H_{14}N_2O_4$	5-CH_3O	CH_3	157.1-158.9 (c)	85.6	59.54	5.38	10.68	59.30	5.19	10.33	----	----	Excess Ac_2O
$C_{14}H_{16}N_2O_4$	5-CH_3O	C_2H_5	141.1-142.6	58.1	60.86	5.84	10.14	60.74	5.94	10.17	----	----	5 eq. anhydride
$C_{15}H_{18}N_2O_4$	5-CH_3O	C_3H_7	132-133.5	65.3	62.06	6.25	9.65	61.96	6.17	9.31	----	----	6 eq. anhydride
$C_{13}H_{14}N_2O_4$	4-CH_3O	CH_3	208.5-210 (e)	66	59.54	5.38	10.68	59.38	5.22	10.41	----	----	3 eq. Ac_2O; 0.5 vol. C_5H_5N (25°)
$C_{14}H_{16}N_2O_4$	4-CH_3O	C_2H_5	180-181.5 (c)	52.1	60.86	5.84	10.14	60.79	5.76	10.16	----	----	10 eq. anhydride
$C_{15}H_{18}N_2O_4$	4-CH_3O	C_3H_7	161-163 (e)	78.5	62.06	6.25	9.65	62.35	6.11	9.98	----	----	5 eq. anhydride + 2 eq. C_5H_5N (70°)

(a) Recrystallized from hot ethyl acetate:ether (1:4). (b) Plieninger (14) reports a m.p. of 187°. (c) Red melt. (d) Decomposition and effervescence. (e) Brown decomposition. (f) Doublet.

TABLE IV

Substituted 1,3-Dihydro-4*H*-furo[3,4-*d*]-1,3-benzodiazepin-3-ones



Formula	Compound	R	R′	Acidic conditions (a)	Reaction time (min.)	M.p. °C	Yield (%)	Analysis Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
$C_{12}H_{10}N_2O_2$·HCl	XI (b)	CH_3	H	40 ml. (3*N*)	10	263-265.1 (c)	91.5	57.49	4.42	11.17	57.56	4.40	11.34
$C_{13}H_{12}N_2O_2$·HCl	XII	C_2H_5	H	50 ml. (4*N*)	35	259.5-262 (c)	83.1	58.98	4.95	10.58	58.61	4.88	10.33
$C_{14}H_{14}N_2O_2$·HCl	XIII	C_3H_7	H	40 ml. (3*N*)	80	255.1-257 (c)	86.2	60.32	5.42	10.05	60.23	5.43	10.06
$C_{17}H_{12}N_2O_2$·HCl	XIV	C_6H_5	H	80 ml. (6*N*)	180	248.1-249.8 (c)	79.5	65.28	4.19	8.95	65.48	4.22	9.28
$C_{13}H_{12}N_2O_2$·HCl·H_2O	XV (d)	CH_3	9-Me	110 ml. (3*N*)	5	282.9-284.1 (c)	95.5	55.22	5.35	9.91	55.43	5.41	10.00
$C_{14}H_{14}N_2O_2$·HCl	XVI	C_2H_5	9-Me	75 ml. (3*N*)	40	254-256.1 (c)	86.2	60.32	5.42	10.05	60.05	5.38	10.41
$C_{15}H_{16}N_2O_2$·HCl	XVII	C_3H_7	9-Me	95 ml. (3*N*)	25	272.5-274 (c)	>95	61.60	5.81	9.58	61.83	6.08	9.46
$C_{13}H_{12}N_2O_3$·HCl	XVIII	CH_3	9-OCH_3	70 ml. (3*N*)	45	266-268 (c)	69.1	55.62	4.67	9.98	55.51	4.71	9.85
$C_{14}H_{14}N_2O_3$·HCl·H_2O	XIX (d)	C_2H_5	9-OCH_3	80 ml. (3*N*)	25 (+ 120 at 5°)	247.2-249 (c)	83.8	53.76	5.48	8.95	53.36	5.18	9.10
$C_{15}H_{16}N_2O_3$·HCl	XX	C_3H_7	9-OCH_3	60 ml. (4*N*) (40°)	20	236.2-237.7 (c)	91.5	58.35	5.55	9.07	58.10	5.40	9.00
$C_{13}H_{12}N_2O_3$·HCl	XXI	CH_3	8-OCH_3	40 ml. (3*N*)	12	285-286 (c)	44.5	55.62	4.67	9.98	55.38	4.66	9.81
$C_{14}H_{12}N_2O_3$·HCl	XXII	C_2H_5	8-OCH_3	55 ml. (3*N*)	25	259-261 (e)	69	57.05	5.13	9.50	56.76	5.38	9.15
$C_{15}H_{16}N_2O_3$·HCl·H_2O	XXIII (d)	C_3H_7	8-OCH_3	90 ml. (5*N*) (b)	15	229-230.9 (e)	51.5	58.35	5.55	9.07	57.92	5.40	9.44

(a) Volumes of acid/10 g. of acyl precursor (Normality); room temperature. (b) Plieninger (8) reported 198° as the m.p. of the base. No constants were given for the hydrochloride salt. Free base, m.p. 201-202.5° (dec.). (c) Decomposition. (d) Analyzed as the monohydrate. (e) Recrystallized from cold absolute ethanol:ether (2:1). (f) Conditions at 80°; treat clear filtrate with solid potassium carbonate to *p*H 4.5 and chill to 5° for 10 hours.

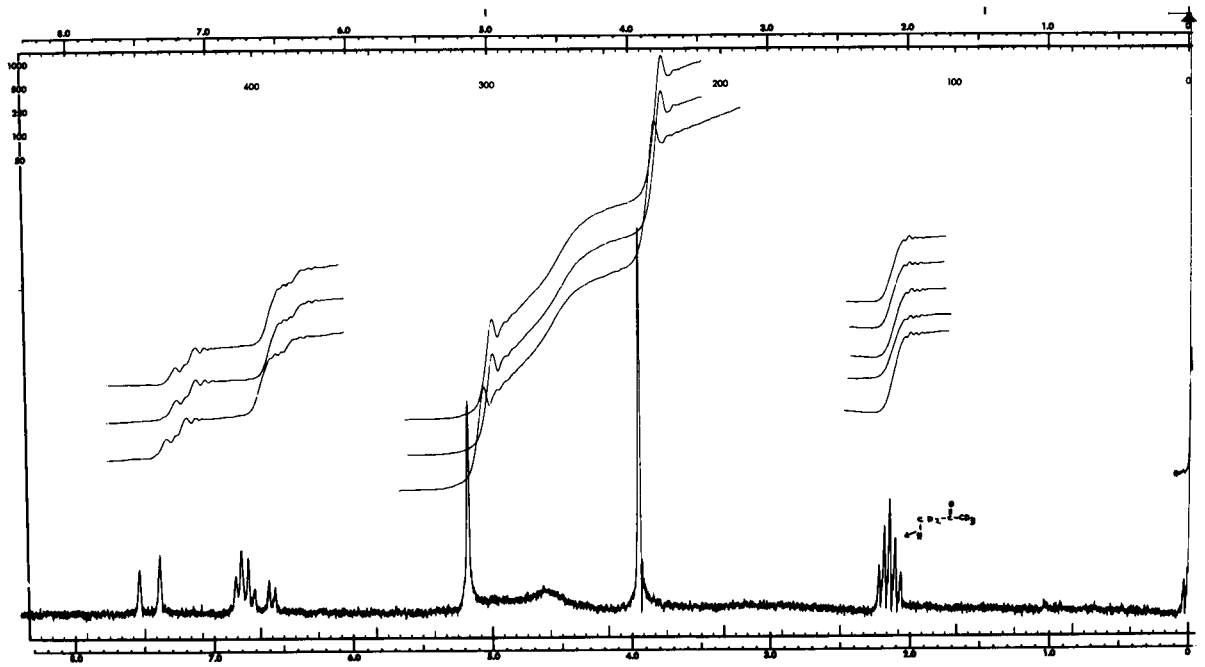


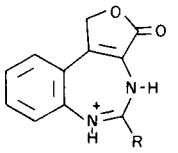
Figure 2. 60 MHz Spectrum of 3-Imino-4-(2-amino-5-anisyl)tetrahydro-2-furanone Hydrochloride in Deuterioacetone.

α-imino lactone ring. We have, however, depicted our compounds as α-imino types throughout in conformance with Plieninger's (8,14) original structure classification.

In further support of our interpretation of the NMR data relative to compound VII, VIII, and IX, it should be noted that compound VII would probably show a greater downfield shift in the CH_3O- position than the 0.1 ppm shift noted for compound VIII *vs.* IX.

The analytical data for the substituted 1,3-dihydro-4*H*-furo[3,4-*d*]-1,3-benzodiazepin-3-ones (I) prepared appears in Table IV. All of the compounds were highly colored and were separated in the final reaction as hydrated compounds. In all cases, dry solids were obtained upon recrystallization and vacuum drying. In Plieninger's original paper (8), a brief mention was made concerning the instability of the hydrochloride salt of XI in boiling water. This point was not elaborated upon and at first glance one might tend to assign a reasonable stability to the compound. Whatever the reason for the instability, the point of interest concerning the aqueous decomposition is that water promotes cleavage of the diaza ring back to the original acyl derivative at room temperature in a very short period of time. We have, however, found the lactone ring to be very stable, requiring high concentrations of base for several hours to effect any decomposition.

The aqueous instability of this system is undoubtedly a function of the inability of the positive charge to be suitably delocalized. One might extrapolate that the 4*H*-1,3-benzodiazepine system contains a hetero ring which is non-planar, the puckered form exhibiting a large degree of double bond localization between the C-5 and C-6 positions. This fact, coupled with the known lability of the -C=N- group toward nucleophilic attack in solution, lends credence to the relative instability of the system to water. The localized structure (X) is peculiar to the



X

system; structurally, a similar type form is obviously absent in the 1,4-benzodiazepines and in the dihydro-1,3-types reported by Rodriquez (10). The mechanism and kinetics of the aqueous decomposition of selected derivatives of I will be described in a subsequent paper.

With regard to the aqueous lability of the methoxy-substituted compounds in this study, it was found that extensive drying of the crude materials was essential prior to recrystallization. Failure to dry the compounds resulted in extensive degradation during recrystallization from absolute ethanol, the heat required and moisture promoting both degradation and free base formation.

EXPERIMENTAL (12)

Tetrahydro-2-furanone-3-(4-tolyl)hydrazone.

Fifty g. (0.47 mole) of *p*-toluidine in 400 ml. of 6*N* hydrochloric acid at 0-5° was treated portion-wise with a cold solution of 35 g. of sodium nitrite in 90 ml. of water. The mixture was stirred in an ice-salt bath for 15 minutes, then added to 60 ml. of 2-acetylbutyrolactone in a mixture of 180 ml. of water and 200 ml. of pyridine at 0° over a period of 2.5 hours. The resulting yellow slurry was stirred at 15° for 0.5 hour, 3 hours at room temperature, and filtered with suction. The cake was air dried, washed with one liter of cold acetic acid, macerated with hot (60°) acetic acid for 0.5 hour, filtered and the air dried solid vacuum dried at 45° overnight to yield 87.0 g. (0.43 mole) (91.4%) of the yellow hydrazone, m.p. 247.5-249° (dec.).

3-Imino-4-(2-amino-4-tolyl)tetrahydro-2-furanone Hydrochloride.

Forty g. (0.2 mole) of tetrahydro-2-furanone-3-(4-tolyl)hydrazone was mixed with 300 ml. of glacial acetic acid in a 1-liter round bottom flask equipped with a condenser, thermometer, gas delivery tube, and a mechanical stirrer. Anhydrous hydrochloric acid was rapidly added to the well stirred slurry until the temperature rose to 76°. Gas introduction was continued until the temperature dropped 10°. The amber solution was stirred until cool, and allowed to stand at room temperature overnight. The imino-amine hydrochloride was precipitated by adding the amber acidic solution in 50 ml. portions to 500 ml. fresh portions of anhydrous ether. The separated solids were removed by filtration, dried by suction, combined, and recrystallized from acetone:ether. The yield was 42 g. (0.18 mole) (98.2%), m.p. 190-191° (dec.).

The recrystallized salt (16.2 g.) (0.07 mole) was dissolved in 250 ml. of water, treated with a saturated solution of potassium carbonate to a *p*H of 7.5, and stirred for 0.5 hour at 5°. The precipitated free base was suction filtered, washed with five 50 ml. portions of water, air-dried, and recrystallized from acetone:water to give 13.8 g. (0.067 mole) of free base (96%), m.p. 129.5-131°, as a bland yellow-white microcrystalline solid.

3-Imino-4-(2-propionamido-5-anisyl)tetrahydro-2-furanone.

Sixteen g. (0.073 mole) of 3-imino-4-(2-amino-5-anisyl)tetrahydro-2-furanone and 60 ml. of propionic anhydride was mixed in a 125 ml. round bottom flask and stirred vigorously until a clear solution was obtained and spontaneous heating occurred. The solution became cloudy, was cooled with stirring in an ice-salt bath for 3 hours, and the amber suspension was filtered. The tan solid was washed with ten 50 ml. portions of water, and dried at 40° and 5 mm. for 5 hours to give 11.8 g. (0.043 mole) of white solid (58.1%), m.p. 141.1-142.6°, after recrystallization from ethanol (60°):water.

5-Ethyl-9-methoxy-1,3-dihydro-4*H*-furo[3,4-*d*]-1,3-benzodiazepin-3-one Hydrochloride.

Five g. (0.018 mole) of 3-imino-4-(2-propionamido-5-anisyl)-tetrahydro-2-furanone was mixed with 40 ml. of 3*N* hydrochloric acid in a 75 ml. glass stoppered Erlenmeyer flask, and shaken vigorously for 25 minutes at room temperature. The mixture was refrigerated for 2 hours, and the reddish-orange suspension was collected by filtration, washed with five 75 ml. portions of ether, air-dried, and then placed in a vacuum desiccator over calcium chloride for 18 hours. The resulting solid was recrystallized from anhydrous ethanol:ether (cold) and dried at 40° and 5 mm. for 10 hours to give 4.5 g. (0.15 mole) of orange-red microcrystals, m.p. 247.2-249° (dec.).

3-Imino-4-[3-(phenylureido-2-phenyl)]tetrahydro-2-furanone (IV).

Three and a half g. (0.018 mole) of II-base (X=H) in 20 ml. of acetonitrile contained in a 50 ml. round bottom flask, was treated with 2.2 g. (0.018 mole) of phenylisocyanate with constant stirring. The temperature of the mixture rose to 54°, then spontaneously cooled. After 10 minutes of stirring, a white solid separated and the mixture solidified. Additional (15 ml.) acetonitrile was added, stirring was continued for 10 minutes to obtain an evenly distributed suspension. The solid was removed by filtration, washed with 50 ml. of cold acetonitrile and dried to give 3.2 g. (0.011 mole) (55.6%) of fine white crystals. An analytical sample recrystallized from hot ethyl acetate:ether (1:4) melted at 193.5-194.2°.

3-Imino-4-[3-(butylureido-2-phenyl)]tetrahydro-2-furanone (V).

Compound II-base (X=H), 4.7 g. (0.025 mole) in a 50 ml. round bottom flask was warmed to 55°, mixed with 7.5 g. (3.1 molar equivalents) of *n*-butylisocyanate, stirred, and while stirring treated dropwise with acetonitrile (at 50°) until a light amber solution was obtained (20 ml.). The heat was removed and the mixture was stirred for 20 hours at room temperature. The solution was transferred to an Erlenmeyer flask, diluted with ether with intermittent swirling, until a total volume of about 80 ml. was reached. The gum which settled was separated by pouring off the solvent. The amber gum was dissolved in 100 ml. of hot ethyl acetate, the solution was evaporated under pressure to 25 ml. and cooled to -20° for three days. The cold suspension was filtered and the tan product was washed with several 50 ml. portions of anhydrous ether. Air-drying and recrystallization from hot ethyl acetate:ether (1:4) gave a white needle-shaped crystalline product, m.p. 136.4-138°, 3.7 g. (0.013 mole) (50.8%).

5-Phenylamino-1,3-dihydro-4*H*-furo[3,4-*d*]-1,3-benzodiazepin-3-one Hydrochloride (VI·HCl).

Three g. (0.010 mole) of IV was mixed with stirring with 34 g. of polyphosphoric acid and slowly warmed until all of the solid had dissolved. The mixture was then heated quickly to 130-140° and maintained at that temperature for 20 minutes with stirring. The dark mixture was cooled to about 90°, mixed with 85 ml. of water at 90°, stirred and scratched while slowly cooling to room temperature. The dark-green suspension was vacuum filtered, and the residue was dried, and partially purified by washing with 200 ml. of ether.

The crude phosphate salt, m.p. 286-288° (dec.), 2.5 g. (0.0067 mole) (67%), was triturated with 20 ml. of 10% aqueous sodium hydroxide until a deep red-brown suspension was obtained. The mixture was cooled to 5° for 30 minutes, filtered, the wet cake obtained was washed with 60 ml. of water at 5°, and vacuum dried for 15 hours at 40°. The crude dry solid was mixed at 45° with 35 ml. of 6*N* hydrochloric acid, stirred vigorously at 40-45° for 6 hours, then refrigerated overnight (14 hours). The solid which separated was filtered off, washed extensively with ether, dried by suction and vacuum dried at 45° for 24 hours. The yield of crude VI-hydrochloride was 1.4 g. (0.0042 mole). A sample recrystallized from anhydrous ethanol:ether melted at 261-263.2° (dec.).

Anal. Calcd. for $C_{17}H_{15}ClN_3O_2$: C, 62.10; H, 4.60; N, 12.78. Found: C, 62.41; H, 4.71; N, 13.20.

REFERENCES

(1) All inquiries should be addressed to Vincent S. Venturella.
(2) Present address: Hoffmann-La Roche Inc., Nutley, N. J.
(3) Present address: Wyeth Laboratories, West Chester, Pa.
(4) L. H. Sternbach in "Psychopharmacological Agents", Vol. 1, M. Gordon, Editor, Academic Press Inc., New York, N. Y.,

1965, pp. 158-161.

(5) W. Ried and A. Draisbach, *Chem. Ber.*, **92**, 949 (1959); W. Ried and E. Torinus, *ibid.*, **92**, 2902 (1959).

(6) J. Thiele and G. Steimmig, *ibid.*, **40**, 955 (1907).

(7) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962); S. C. Bell, T. Sulkowski, C. Gochman and S. J. Childress, *ibid.*, **27**, 562 (1962); R. I. Fryer, R. A. Schmidt and L. H. Sternbach, *J. Pharm. Sci.*, **53**, 264 (1964); L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111, 4936 (1961).

(8) H. Plieninger and I. Nogrady, *Chem. Ber.*, **88**, 1965 (1955).

(9) G. deStevens and M. Dughi, *J. Am. Chem. Soc.*, **83**, 3087 (1961).

(10) H. R. Rodriquez, B. Zitko and G. deStevens, *J. Org. Chem.*, **33**, 670 (1968); this publication appeared after the completion of the present study.

(11) R. J. Owellen, J. A. Fitzgerald, Bernice M. Fitzgerald, D. A. Welsh, D. M. Walker and P. L. Southwick, *Tetrahedron Letters*, No. 18, 1741 (1967).

(12) Details given for the preparation of the *p*-tolylhydrazone of γ-butyrolactone, general compounds I, II, and III are typical of members of the series given in Tables I, IV, II, and III, respectively. All m.p.'s are corrected. Infrared measurements were made using a PE 137 or Beckman IR-7 spectrometer; NMR spectra were obtained on a Varian Model A60-A, courtesy of Mr. Ronald Rodabaugh of the Department of Chemistry. U.V. and visible spectral measurements were obtained using the B&L 505, Cary Model 15 and Beckman DU-2 (modified with a Gilford Model 2000) spectrometers.

(13) A. Duffin, *J. Chem. Soc.*, 3470 (1955).

(14) H. Plieninger, *Chem. Ber.*, **83**, 273 (1950).

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