Benzazepinones. Synthesis of the Monoaza Analog of Diazepam, and the Correct Structure of the Benzoylpropionanilide Cyclization Product

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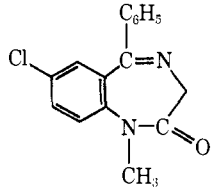
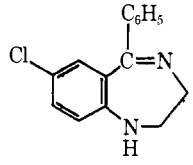
The synthesis of 1,3-dihydro-2*H*-1-benzazepinones is described; the critical step utilizes a specific DDQ-dehydrogenation of an 8-membered ring lactam. The exact monoaza analog of diazepam was prepared utilizing selective NCS in DMF halogenation. A previous literature compound said to be a 2*H*-1-benzazepinone was shown to be incorrect, and the correct structure of that compound was assigned. The monoaza analog of diazepam did not possess diazepam-like neuropharmacological activity.

Investigation of benzodiazepines related to chlordiazepoxide revealed that the complex functionality of the heterocyclic ring of this drug could be reduced to lactam and imino moieties, as in diazepam (I), with enhancement of antianxiety activity.[1,2] Further structure–activity studies showed that appreciable



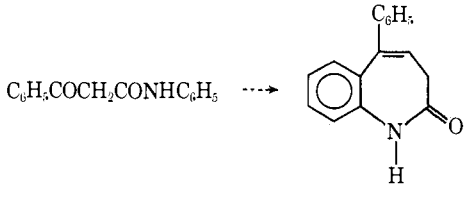
I



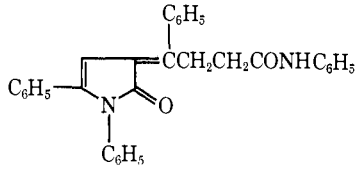
II

pharmacological activity was retained when the lactam carbonyl was replaced by CH_2 as in II.[1,2] The only functional groups in II are the anilino N and the C=N group. The aim of the present study was to determine how the replacement of the imino N of diazepam by CH affected its CNS-depressant activity.

The first reference to the synthesis of this ring system (1,3-dihydro-2*H*-1-benzazepinones) is that of Bertho in 1957.[3] He reported that NH_4Cl catalyzed the cyclization of β-benzoylpropionanilide at 200° to give a yellow product, mp 196–196.5°, to which he assigned the benzazepinone structure **1**. We have now determined that the correct structure of this product is **2**.



1



2

We questioned the original structure assignment of this compound because *N*-methyl-β-benzoylpropionanilide did not undergo reaction under identical conditions, and because no rationalization could be found for the yellow color of Bertho's reaction product. Further, although the catalytic reduction of **1** was reported to yield the dihydro derivative, in our hands the catalytic hydrogenation of the yellow reaction product gave only an oil which in no way resembled a sample of dihydro **1** (mp 180–181°) prepared by an unambiguous alternate route.[4]

The molecular parent ion of the yellow product was found to be 470, double that expected for **1**. The nmr spectrum showed a complex aromatic absorption centered at *ca.* 7.33, a vinyl proton at 5.95, and a pair of triplets centered at δ 2.55 and 3.68 (J = 8.5 Hz) in the ratio of 20:1:2:2. Heating the yellow solid with 48% HBr in glacial AcOH afforded only 2 isolable products: β-benzoylpropionic acid and aniline. Neither of these products is consistent with structure 1.

A search of the literature revealed that, in 1898, Klobb[5] had described the isolation of a yellow compound, mp 195°, as a by-product in the preparation of β-benzoylpropionanilide. His material readily hydrolyzed to β-benzoylpropionic acid and aniline and was assigned structure **2**. More recently[6] it has been shown that the reaction of β-benzoylpropionic acid with ammonium salts gives an analogous product. A possible reaction sequence is shown in Scheme I.[7] It should be noted that *N*-methyl-β-benzoylpropionanilide cannot undergo a ring closure of this sort.

The synthesis of authentic **1** (and ring halogenated analogs) was undertaken, with first consideration given to ring closure reactions.

(1) For reviews see L. H. Sternbach, L. O. Randall, and S. R. Gustafson in "Psychopharmacological Agents," Vol. I, M. Gordon, Ed., Academic Press, New York, N. Y., 1964, p 137; S. J. Childress, "Medicinal Chemistry," Vol. II, A. Burger, Ed., Wiley-Interscience, New York, N. Y., 1970, p 1503.

(2) G. Zbinden and L. O. Randall, *Advan. Pharmacol.*, **5**, 213 (1967).

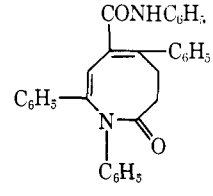
(3) A. Bertho, *Chem. Ber.*, **90**, 29 (1957).

(4) L. H. Werner, S. Ricca, A. Rossi, and G. deStevens, *J. Med. Chem.*, **10**, 575 (1967).

(5) M. T. Klobb, *Bull. Soc. Chim. Fr.*, **19**, 389 (1898).

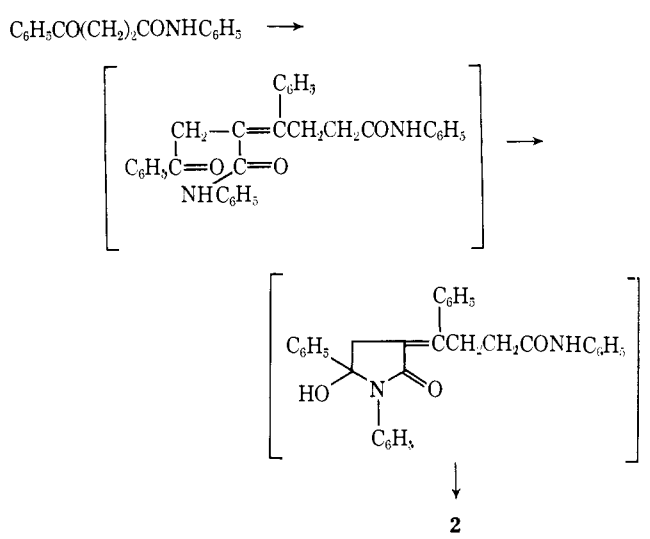
(6) H. Fiesselmann and W. Ehmann, *Chem. Ber.*, **91**, 1713 (1958); A. Treibs, K. Jacob, and A. Dietl, *Justus Liebigs Ann. Chem.*, **702**, 112 (1967).

(7) An alternative formulation which also accommodates all the physical data is the 8-membered ring i. This possibility seems highly unlikely when one considers the relative ease of formation of a 5-membered ring as compared to an 8-membered ring.



i

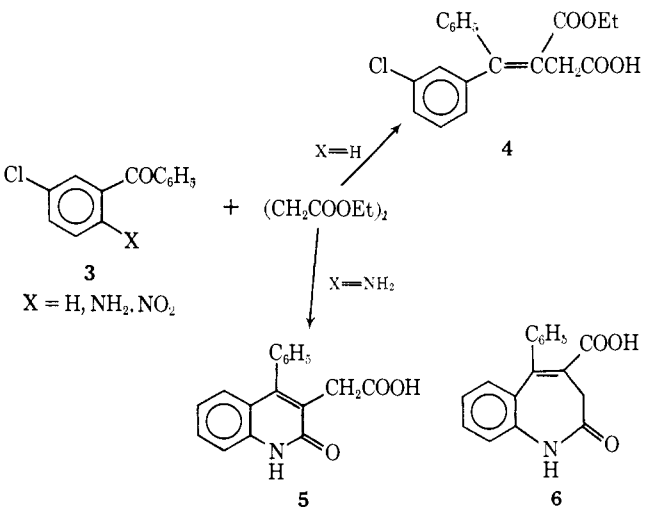
SCHEME I



Attempts to cyclize β-benzoylpropionanilide to **1** using other catalysts failed. In order to avoid the formation of **2**, *N*-methylsuccinanilide was treated similarly under various ring closure conditions. The only isolable product was the bis(anilide); attempted cyclization of this failed even under vigorous conditions.

Intermolecular condensation reactions were studied. Attempted utilization of Wittig-type intermediates [prepared from *o*-(β-chloropropionamido)benzophenone] led instead to disproportionation products. In an alternative approach, the Stobbe condensation was investigated utilizing the condensation of aryl ketones with succinic esters. This reaction normally proceeds to give excellent yields of mono ester (**4**, Scheme II),[8]

SCHEME II



which are potential precursors of benzazepinones. However, when the reaction was carried out on the ortho-substituted ketone **3**, X = NH_2, direct conversion to a 6-membered carbostyril, **5**, resulted, rather than conversion to the benzazepinone **6**. The structure of **5** is assigned on the basis of its failure to decarboxylate even under strenuous conditions, its spectral similarity to carbostyrils, and its dissimilarity to the benzazepinones ultimately prepared. When the reaction was attempted using **3**, X = NO_2 or NHAc, no condensation occurred.

The dihydrobenzazepinone **8**[4] (Scheme III) was obtained as the sole isomer on rearrangement of the oxime of **7**. In contrast, Curtius reaction on the tetralone gives a mixture of the isomeric lactams[4] that was very difficult to separate.

The dihydrobenzazepinone **8** resisted all attempts at dehydrogenation using the usual agents (S, Se, Pd, SeO_2, MnO_2) under a variety of vigorous conditions. However, the comparatively mild oxidizing agent dicyanodichloroquinone (DDQ) gave a 75% yield of **1** as a white solid, mp 200–201°, *m/e* 235.

Among the other routes investigated for introduction of the double bond into **8** was one involving attempted benzylic halogenation–dehalogenation by reaction with *N*-chlorosuccinimide in DMF. Only ring halogenation occurred, giving a good yield of **9**. The position of the Cl on the benzo ring is consistent with nmr data and the pattern of NCS chlorination established for carbostyrils.[9] This proved to be very fortunate because the exact monoaza analog of diazepam requires a Cl at this position, and the reaction sequence just described for the synthesis of **1** could not be applied directly to the synthesis of the Cl derivative since cyclization of 3-phenyl-3-(*m*-chlorophenyl)butyric acid would have led to preferential cyclization on to the unsubstituted benzene ring giving the 5-(*p*-chlorophenyl) analog of **8**. DDQ dehydrogenation of **9** gave the benzazepinone **10** which on methylation gave **12** the desired monoaza analog of diazepam.

As indicated in Scheme III, the dehydrogenation and alkylation steps can be reversed (**9**→**11**→**12**).

The reaction of **1** with NCS gave a Cl compound which had a mp similar to that of **10**, but which unexpectedly proved to be different from **10**. This new compound (**13**) was found to have been chlorinated at the 4 position as shown by the disappearance of the δ 6.3 vinyl proton in the nmr. As can be seen from Scheme III, whenever the olefinic linkage at Δ^4 is present, vinyl halogenation takes preference over ring halogenation.

Replacing NCS by HCl and $NaClO_2$ or by *tert*-BuOCl gave only complex mixtures.

Attempts to extend the DDQ dehydrogenation to the synthesis of the parent 5-unsubstituted Δ^4-benzazepin-2-one failed. 4,5-Dihydro-1-benzazepin-2-one[10] (**18**) was recovered unchanged even after extensive heating with DDQ. However, NCS halogenation of **18** proceeded smoothly to give the 7-Cl derivative (**23**, R = H) and a small amount of *N*-chloro-4,5-dihydro-1-benzazepin-2-one. This was the only time that an *N*-chloro product was obtained.

A similar sequence of events with respect to ring *vs.* vinyl halogenation was observed with the *N*-Me derivatives. The various series were interrelated when NCS chlorination of **12** gave the same product (**16**) as obtained by chlorination of **15**.

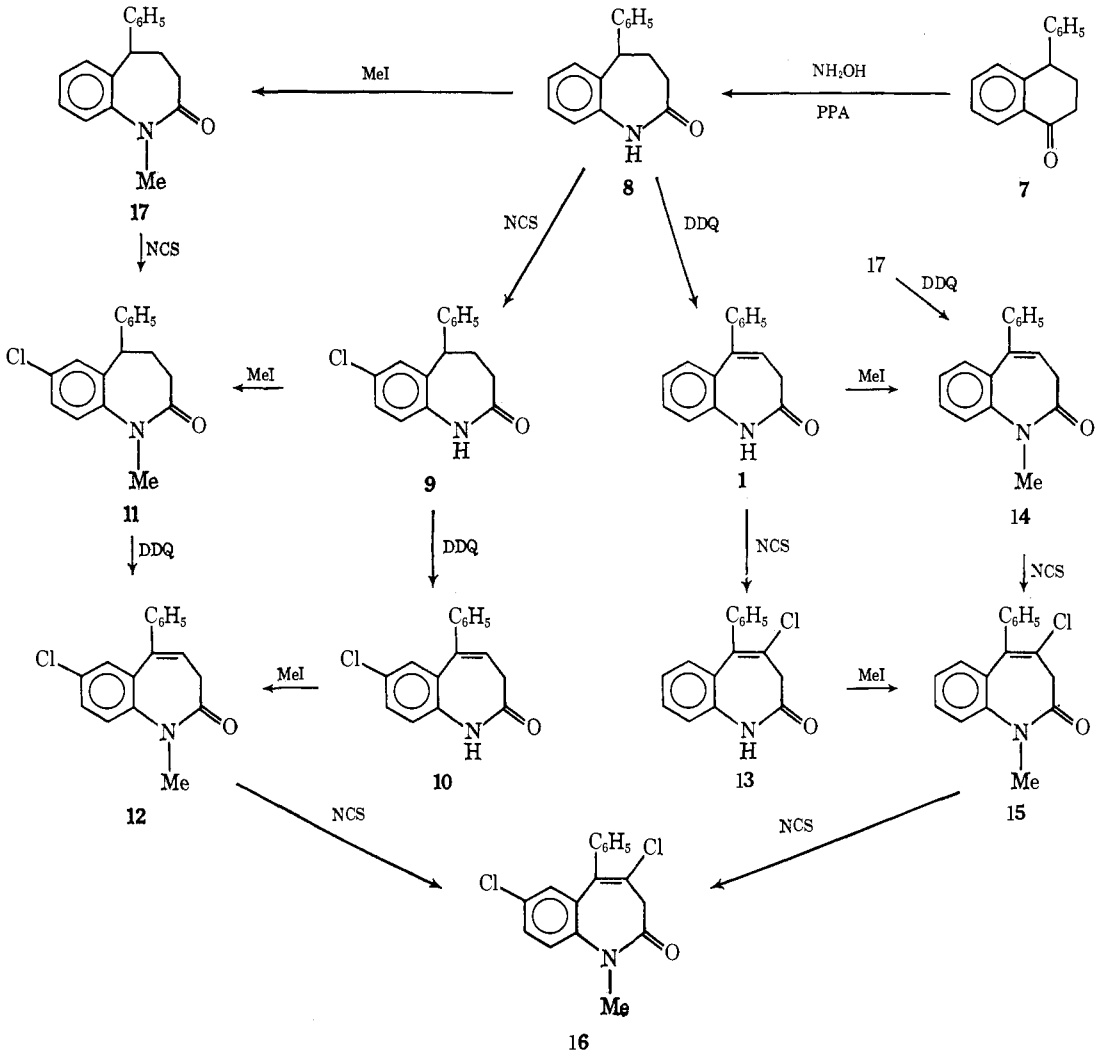
For structure–activity studies, certain of the compounds (**12** and **14**) were reduced to the benzazepines (**19**) with LAH; in others a basic group was introduced (**20** and **21**).

(8) W. S. Johnson and G. H. Daub, *Org. React.*, **6**, 1 (1951).

(9) B. Loev and M. F. Kormendy, *J. Org. Chem.*, **30**, 3163 (1965).

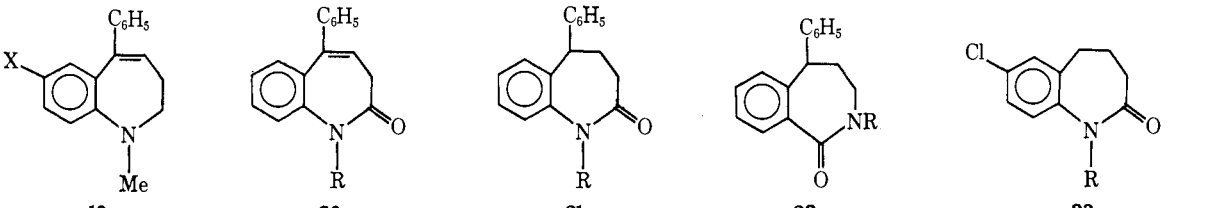
(10) L. G. Donaruma and W. Z. Heldt, *Org. React.*, **11**, 57 (1960).

SCHEME III



The lactam isomeric with 8, isolated from the Curtius reaction on the tetralone,[4] was also converted to aminoalkyl derivatives **22** isomeric with **21**.

The compounds were tested for potential anti-



anxiety activity using antipentylenetetrazole activity in the rat[11a] as a measure. The most active compounds proved to be **17**, **19** (X = Cl), and **23** (R = H) (which showed 100, 80, and 80% inhibition of seizures at 100, 200, and 200 mg per kg po, respectively), but they were considerably less potent than chlordiazepoxide. None of the other compounds, including the diazepam analog **12**, showed significant antipentylenetetrazole activity and none of the compounds showed significant overt effects at doses below 100 mg per kg po. Compounds **20**, **21**, and **22** (n = 3) were active in inhibiting basal gastric acid secretion in gastric fistula rats[11b] at 50, 50, and 30 mg per kg po, respectively.

(11) (a) F. A. Baron, C. A. Vanderwerf, and D. H. Tedeschi, *J. Med. Chem.*, **10**, 276 (1967); (b) D. A. Brodie, R. W. Marshall, and O. M. Moreno, *Amer. J. Physiol.*, **202**, 812 (1962).

Experimental Section[12]

4-Phenyl-3-carboxymethyl-2-quinolone (5).—EtOH (3.1 ml) was added to NaH (18.2 g of 57% mineral oil suspension) in 108 ml of dry C_6H_6. After H_2 evoln ceased, 50 g of 2-amino-5-chlorobenzophenone followed by 113 g of diethyl succinate were added. A vigorous exothermic reaction occurred. After the mixt was stirred for 3 days, more EtOH and cold AcOH were added, and

(12) Melting points are corrected, boiling points are uncorrected. Elemental analyses were performed by Miss M. Carroll and coworkers of the Analytical and Physical Chemistry Section, Smith Kline and French Laboratories. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

then the mixt was extd with a large vol of Et_2O. When 5% $NaHCO_3$ was added, a solid sepd at the interface; this was filtered giving 13 g of **5**, mp 285° dec. After recrystn from DMF it melted at 290° dec. *Anal.* ($C_{17}H_{12}ClNO_3$) C, H, N, Cl. Attempts to decarboxylate this material thermally or by heating with HBr–HOAc, $PhNMe_2$, or Cu salts gave either no change or total decompn.

5-Phenyl-4,5-dihydro-1-benzazepin-2-one (8).—The oxime of **7** was prepd in 84% yield in the usual manner and used for the Beckmann reaction after 1 recrystn, mp 115–117°. The oxime (85 g) was added portionwise with stirring to 1100 g of PPA preheated to 120°. After 15 min the red-brown soln was poured onto ice and a white solid sepd. The mixt was extd with $CHCl_3$ giving 87.5 g of **8**, mp 177–181°. It was recrystd from MeCN and rinsed with hexane giving 63 g of **11**, mp 180–181.5° (lit.[4] 180–182°). Concn of the filtrate gave an addl 8 g of **8**. No trace of the isomeric 2-benzazepin-1-one was found.

Use of the Schmidt reaction[4] gave a mixt of **8** and the isomeric 5-phenyl-4,5-dihydro-2-benzazepin-1-one, mp 226–228° (lit.[4] mp 226–228°) which could be readily isolated only by "dry-column" chromatography.[13]

DDQ Dehydrogenations.—The benzazepinone (0.1 mole) was added to a soln of 0.125 mole of DDQ in 500 ml of C_6H_6 and the resulting dark soln was heated at reflux for 18 hr. The pptd dichlorodicyanohydroquinone was filtered (mp 315°), and the filtrate was concd. The solid residue was either recrystd from the appropriate solvent or dissolved in Et_2O and passed through a small Florisil column to remove the last traces of DDQ or hydroquinone and then recrystd (see Table I).

TABLE I

Product	% yield	Recrystn solvent	Mp, °C	Anal.
1	77	EtOAc	200–201	C, H, N
10	51	MeCN	211–214	C, H, N, Cl
12	73	*i*-Pr_2O	132–133	C, H, N, Cl
14	67	MeOH–H_2O	91–93	C, H, N

NCS Chlorination Procedure.—NCS (0.1 mole) was added to a soln of 0.1 mole of benzazepinone in a small vol of DMF and the soln was heated on the steam bath for 1 hr, then cooled and dild with H_2O. A white solid sepd and was filtered, dried, and recrystd (see Table II).

N-Alkylations.—A soln of benzazepinone (0.1 mole) in dry DMSO was added slowly with stirring to a suspension of 0.13 mole of NaH in DMSO. After addn was completed, stirring was contd for 0.5 hr, then a soln of Me_2SO_4 or dialkylaminoalkyl halide in dry C_6H_6 was added dropwise at a rapid rate. The mixt was heated for 18 hr on a steam bath and cooled, and a few milliliters of EtOH was added. The mixt was then concd *in vacuo*, H_2O was added, and the soln was extd with Et_2O. The ext was washed with H_2O and concd, and the residue recrystd. In the case of the aminoalkyl-substituted products, the Et_2O layer was extd with dil HCl; then the ext was made basic and extd with Et_2O dried, and concd, and the residue recrystd (see Table III).

TABLE II

Product	% yield	Recrystn solvent	Mp, °C	Anal.
9	58	EtOAc	185–186	C, H, N, Cl
11	30	*i*-Pr_2O	99–101	C, H, N, Cl
13	76	$MeNO_2$	270–272	C, H, N, Cl
15	40	60% EtOH	129–131	C, H, N,
16	58	*i*-Pr_2O	137–139	C, H, N, Cl
23,[a] R = H	61	EtOAc	164.5–167.5	C, H, N, Cl

[a] A small yield of another compd, mp 157–161°, was also isolated from this reaction. It was identified as the *N*-Cl derivative based on anal (C, H, Cl, N) and facile aq hydrolysis to **23**, R = H.

TABLE III

Product	% yield	Recrystn solvent	Mp or bp (mm), °C	Anal.
11	80	*i*-Pr_2O	99–101	C, H, N, Cl
12	*a*			C, H, N, Cl
14	39	Hexane	88–90	C, H, N
15	*a*			
17	76	*i*-Pr_2O	101–103.5	
20, *n* = 2	32	Hexane	99.5–101.5	C, H, N
20, *n* = 3	35	Hexane	93–95	C, H, N
21, *n* = 2	57	*i*-Pr_2O	142–143.5	C, H, N
21, *n* = 3	42	Hexane	66.5–68.5	C, H, N
22, *n* = 3	15	*i*-Pr_2O	114–115	C, H, N
23, *n* = 2	70	Hexane	51–53	C, H, N, Cl
23, *n* = 3	55		127 (0.01 mm)	C, H, N, Cl
23, R = Me	55	Hexane	59–61	C, H, N, Cl

[a] Not detd; tlc isolation; identical with material prepd by alternate route.

1-Methyl-5-phenyl-7-X-2,3-dihydro-1-benzazepine (19, X = H, Cl).—A suspension of 0.4 g of LAH in THF was added slowly to a soln of 4.5 g of **14** in 150 ml of THF and the mixt was then refluxed for 18 hr. A small amt of EtOAc was added, then a little H_2O, and the mixt was filtered and the filtrate concd to give an oil. This was dissolved in CH_2Cl_2 and passed through a small alumina column (1.25 × 10 cm), and the filtrates were collected and concd. The residue crystd giving a 40% yield of **19**, X = H, mp 82–84° (hexane), and 10% yield of **19**, X = Cl, mp 104–106° (hexane). *Anal.* ($C_{17}H_{17}N$) C, H, N and ($C_{17}H_{16}ClN$) C, H, N.

Acknowledgments.—We wish to thank Professor Peter Yates for helpful discussion concerning the structure of **2**, and Edward Macko and William Groves of these laboratories for the biological data.

(13) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967); B. Loev and M. M. Goodman, *Progr. Separ. Purif.*, **3**, 73 (1970).