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THE SYNTHESIS OF SOME 2,4-BENZODIAZEPIN-1-ONES, POTENT C.N.S. AGENTS

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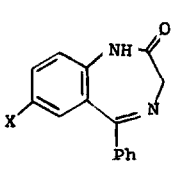
The impressive physiological properties of 1,4-benzodiazepinone derivatives (I) have greatly stimulated synthetic work in this series of heterocyclic compounds over the last two decades. The structure-activity relationship within this new class of highly active C.N.S. drug and manifold structural variations of benzodiazepinone systems have been extensively studied.[1]

It seems therefore rather surprising that no attempts of synthesizing the last remaining isomer, namely 2,4-benzodiazepin-1-one (II) have been reported so far. We are now describing a novel method of preparing these rather elusive compounds.

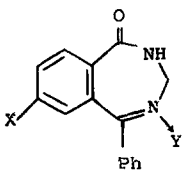
O-Benzoylbenzamide[2] (IIIa) adds formaldehyde in basic media[3] to form N-hydroxymethyl-(2-benzoyl)-benzamide (IIIb) in high yield (85%): m.p. 168/9°. H^1-NMR (DMSO-d_6): δ=7.95-7.20 (m, 9H aromatic), 7.13 (s, NH disappears with D_2O), 5.62 (t, J=7 cps OH which disappears with D_2O), 5.10-4.67 (m, CH_2 which turns to double d 4.82 J=11 cps when treated with D_2O). IR (KBr) 1700-1660, 1620 cm^{-1} (carbonyls). The methylol derivative (IIIb) was treated with $SOCl_2$ in chloroform. N-Chloromethyl-(2-benzoyl)-benzamide (IIIc) was isolated from the reaction mixture in good yield - (85%): m.p. 136/8° crude product. H^1-NMR ($CDCl_3$); δ=8.00-7.20 (m, aromatic H), 5.23 (double d, J=11 cps CH_2), 3.75-3.50 (broad s, NH disappears with D_2O). IR (KBr) 1700-1670, 1620 cm^{-1} (carbonyls).

N-Chloromethyl-(2-benzoyl)-benzamide (IIIc) reacted with aqueous ammonia in dioxan. Chromatography of the crude reaction product over a silica gel column yielded 12% of 5-phenyl-2,3-dihydro-1H-2,4-benzodiazepin-1-one (IIa), m.p. 214° (from EtOAc or dioxan). H^1-NMR (DMSO-d_6): δ=9.17 (t, J=6 cps NH disappears with D_2O), 8.10-7.17 (m, 9H aromatic), 4.75-4.10 (broad s, CH_2).

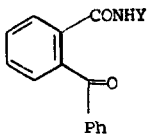
Oxidation of IIa by means of m-chloroperbenzoic acid yielded 40% of 5-phenyl-2,3-dihydro-1H-2,4-benzodiazepin-1-one-4-oxide (IIb), m.p. 215° (From EtOAc). H^1-NMR ($CDCl_3$): δ=8.88 (t, J=7 cps NH), 8.20-8.00 (m, 1H aromatic), 7.72-7.25 (m, 7H aromatic), 7.17-6.90 (m, 1H aromatic), 5.15 (d, J=7 cps CH_2). The oxaziridine derivative (IV) was isolated as a byproduct (10% yield) of this reaction and was identified by its oxidizing properties,[4] m.p. 180°, H^1-NMR ($CDCl_3$): δ=8.20-7.00 (m, 9H aromatic and NH), 5.10-4.60 (m, 1H from $-CH_2-$) 5.05-3.75 (m, 1H from $-CH_2-$).



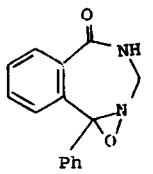
I a) X=H
b) X=Cl



II a) X=H Y=Void
b) X=H Y=O
c) X=Cl Y=Void



III a) Y=H
b) Y=CH_2OH
c) Y=CH_2Cl



IV

Preliminary pharmacological assays revealed that the new benzodiazepinones IIa and IIb do exhibit marked C.N.S. activity especially in the antimetrazol test where they show ED_{50} values of 24, 28 mg/kg respectively when administered per os. These figures come very close to those shown by 1,4-benzodiazepinones unsubstituted at the 7 position (Ia) when submitted to this particular test.[5] In view of these encouraging findings the synthesis of the 7-chloro derivative (IIc) seemed indicated. It was possible to prepare this compound (IIc) by using our newly established route: m.p. 139° H^1-NMR ($CDCl_3$): δ=8.52 (t, J=6 cps NH), 8.12 - 7.18 (m, 8H aromatic), 4.80 - 4.30 (broad s, CH_2). Pharmacological screening of IIc showed the expected higher C.N.S. activity with: ED_{50} at 1.5 mg/kg per os in the antimetrazol test and ED_{40} at 25 mg/kg per os in the maximal electroshock test which puts it clearly in the range of Valium[5] activity.

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References

1. a) G.A. Archer and L.H. Sternbach, Chem.Rev. 68, 747 (1968).
b) L.H. Sternbach, Angew.Chem.Internat.Edit. 10, 34 (1971).
2. C.L. Hewett, L.J. Lermit, H.T. Openshaw, A.R. Todd, A.H. Williams and F.N. Woodward, J.Chem.Soc. 292 (1948).
3. H.E. Zaugg, W.B. Martin in "Organic Reactions" Vol. XIV A.C. Cope Ed. John Wiley and Sons, Inc. New York, N.Y. 1965, p. 130.
4. W.D. Emmons, J.Am.Chem.Soc. 79, 5739 (1957).
5. L.H. Sternbach, L.O. Randell, R. Banzinger, and H. Lehr in "Drugs Affecting the Central Nervous System" Vol. 2 A. Burger Ed., Marcel Dekker, Inc. New York, N.Y. 1968 p. 237.