1,4-BENZODIAZEPINES AND THEIR CYCLIC HOMOLOGS AND ANALOGS.

30.* SYNTHESIS AND PROPERTIES OF 3- AND 7-AMINO-5-PHENYL-1,2-DIHYDRO-3H-1,4-BENZODIAZEPIN-2-ONES

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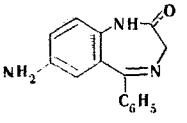
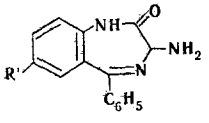
UDC 547.892

The transformations (acylation, condensation with aldehydes, and diazotization) of 7- and 3-amino-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones are examined. It is shown that the action of P_2S_5 on 3-acetamidobenzodiazepinone leads to replacement of the oxygen atom of the acetyl group by a sulfur atom. The polarographic reduction of 7-arylideneamino-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones was studied.

2-Amino-5-phenyl-3H-1,4-benzodiazepines are 1,4-benzodiazepine derivatives that have been well studied [1-3]. Less study has been devoted to 3- and 7-amino-1,2-dihydro-3H-1,4-benzodiazepin-2-ones, although methods for the synthesis of I and IIa and some of their properties have been described [4, 5].



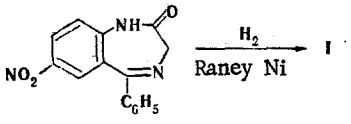
I



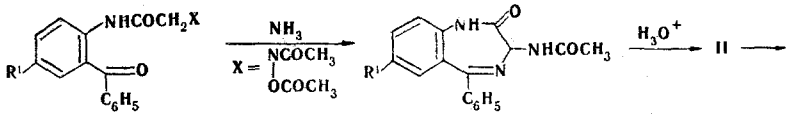
II

II a R^1=Cl; b R^1=Br; c R^1=H; d R^1=CH_3

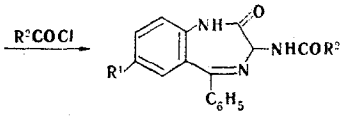
We synthesized I by hydrogenation of nitrazepam III over Raney nickel [4]. Compounds II were obtained by the method in [5] by the action of an alcohol solution of ammonia on 2-[2-(N-acetoxyacetamido)acetamido]benzophenones (IV) with subsequent acid hydrolysis of the 3-acetamidobenzodiazepinones V.



III



IV, VI–VIII V



IX

IV X=$NCOCH_3$ (|) $OCOCH_3$; VI X=NHOH; VII X=Cl; VIII X=I; IX a R^2=CH_3; R^1=Cl; b R^2=3,4,5-$(OMe)_3C_6H_2$, R^1=Cl; c R^2=Ad, R^1=Cl

*See [8] for communication 29.

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0009-3122/79/1504-0447$07.50

TABLE 1. 2-Aminobenzophenone Derivatives

Compound	mp, °C *	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
VIIa	122	58,4	3,3	4,6	$C_{15}H_{11}Cl_2NO_2$	58,6	3,5	4,6	70
VIIb	135—137	51,0	3,0	4,2	$C_{15}H_{11}ClBrNO_2$	51,4	3,1	4,0	68
VIIc	94—95	67,0	5,0	4,7	$C_{16}H_{14}ClNO_2$	66,8	4,8	4,8	86
VIId	110—111	66,0	4,6	5,1	$C_{15}H_{12}ClNO_2$	65,8	4,4	5,0	58
VIIIa	127	45,4	2,8	3,3	$C_{15}H_{11}ClINO_2$	45,1	2,7	3,1	80
VIIIb	123—124	40,5	2,0	3,5	$C_{15}H_{11}BrINO_2$	40,5	2,2	3,2	91
VIIIc	90—91	49,2	3,0	3,8	$C_{15}H_{12}INO_2$	49,4	3,3	3,8	88
VIIId	112—114	50,6	3,7	3,7	$C_{16}H_{14}INO_2$	50,8	3,7	3,6	85
VIa	128—129	59,0	4,2	9,1	$C_{15}H_{13}ClN_2O_3$	59,2	4,2	9,0	68
VIb	123—124	51,4	3,7	8,1	$C_{15}H_{13}BrN_2O_3$	51,5	3,7	8,0	65
VIc	114—116	66,4	5,0	10,7	$C_{15}H_{14}N_2O_3$	66,6	5,2	10,4	77
VId	118—120	67,4	5,6	9,8	$C_{16}H_{16}N_2O_3$	67,6	5,6	9,8	64
IVa	155—156	58,7	4,4	7,1	$C_{19}H_{17}ClN_2O_5$	58,8	4,4	7,2	83
IVb	139—140	52,8	4,0	6,4	$C_{19}H_{17}BrN_2O_5$	52,6	3,9	6,5	70
IVc	234—235	64,6	5,5	7,8	$C_{19}H_{18}N_2O_5$	64,4	5,1	7,9	60
IVd	244—245	65,0	5,6	7,6	$C_{20}H_{20}N_2O_5$	65,2	5,4	7,6	45

*The following melting points were found in the literature: VIIa 123°C [5]; VIIIa 125-127°C [5]; VIa 129-131°C [5], and IVa 152-155°C [5].

TABLE 2. Amino and Acylamino Derivatives of 1,2-Dihydro-3H-1,4-benzodiazepin-2-ones

Compound	mp, °C *	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
Va	273—274	62,2	4,6	12,8	$C_{17}H_{14}ClN_3O_2$	62,4	4,3	12,8	47
Vb	293—294	54,8	4,0	11,1	$C_{17}H_{14}BrN_3O_2$	54,8	3,8	11,3	41
Vc	222—224	69,6	5,4	14,5	$C_{17}H_{15}N_3O_2$	69,6	5,1	14,3	42
Vd	214—216	70,2	5,8	13,5	$C_{18}H_{17}N_3O_2$	70,3	5,5	13,6	40
IIa	205—206	63,2	4,6	14,9	$C_{15}H_{12}ClN_3O$	63,1	4,2	14,7	45
IIb	210—211	50,2	3,8	12,5	$C_{15}H_{12}BrN_3O$	50,4	3,6	12,7	42
IIc	178—179	72,0	5,4	16,4	$C_{15}H_{13}N_3O$	71,7	5,1	16,7	62
IId	200—202	72,6	5,9	15,4	$C_{16}H_{15}N_3O$	72,4	5,7	15,8	60
IXc	264	70,1	5,8	9,6	$C_{26}H_{25}ClN_3O_2$	70,0	5,6	9,4	72
IXb	267	62,9	5,0	9,0	$C_{25}H_{22}ClN_3O_5$	62,6	4,6	8,7	63
X	284	60,2	4,4	12,5	$C_{17}H_{14}ClN_3OS$	60,0	4,0	12,3	48

*The following melting points were found in the literature: Va 272-274°C [5], and IIa 200-206°C [5].

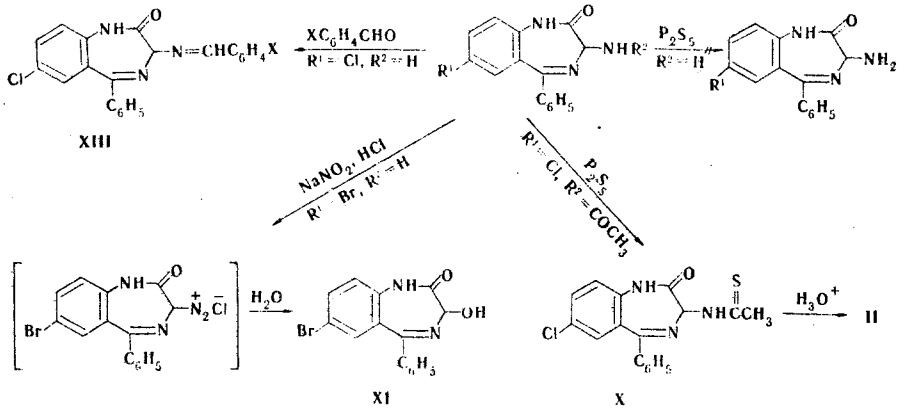
Compounds IV were obtained by the action of acetic anhydride on 2-(hydroxyamino)acetamidobenzophenones (VI), which in turn were obtained by successive replacement of the chlorine atom in 2-chloroacetamidobenzophenones VII by iodine and the iodine atom in 2-iodoacetamidobenzophenones VIII by a hydroxyamino group. The intermediates (VI-VIII and IV) are presented in Table 1, and II and V are presented in Table 2. The action of acetyl chloride

TABLE 3. Aldimino-1,2-dihydro-3H-1,4-benzodiazepin-2-ones

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
XIIIa	185—187	70,4	4,4	11,2	$C_{22}H_{16}ClN_3O$	70,7	4,3	11,2	30
XIIIb	180—182	64,4	3,6	10,0	$C_{22}H_{15}Cl_2N_3O$	64,7	3,7	10,3	40
XIIIc	197—200	58,1	3,3	9,2	$C_{22}H_{15}BrClN_3O$	58,3	3,3	9,3	40
XIIId	156—157	63,0	3,2	13,2	$C_{22}H_{15}ClN_4O$	63,0	3,6	13,4	25
XIVa	168—170	77,6	5,0	12,4	$C_{22}H_{17}N_3O$	77,8	5,0	12,4	61
XIVb	192—193	70,8	4,3	11,2	$C_{22}H_{16}ClN_3O$	70,7	4,3	11,2	72
XIVc	196—198	63,0	3,8	10,2	$C_{22}H_{16}BrN_3O$	63,1	3,8	10,0	50
XIVd	278—280	68,6	4,4	14,5	$C_{22}H_{16}N_4O_3$	68,7	4,2	14,7	50
XIVe	237—238	68,5	4,2	14,5	$C_{22}H_{16}N_4O_3$	68,7	4,2	14,7	37
XIVf	154—156	68,5	4,4	14,7	$C_{22}H_{16}N_4O_3$	68,7	4,2	14,7	55
XIVg	276—277	74,5	4,6	11,8	$C_{22}H_{17}N_3O_2$	74,3	4,8	11,7	70
XIVh	240—243	75,2	5,6	14,7	$C_{24}H_{22}N_4O$	75,4	5,8	14,7	50
XIVi	255—257	76,2	6,3	13,4	$C_{26}H_{26}N_4O$	76,0	6,3	13,6	40
XIVj	168—169	72,8	4,6	12,5	$C_{20}H_{15}N_3O_2$	72,9	4,5	12,7	39

on II leads to 3-acetamidobenzodiazepinones that are identical to those obtained from IV; this may be regarded as a chemical confirmation of their structures.

The 1,2-dihydro-3H-1,4-benzodiazepin-2-ones are easily converted to the corresponding thiolactams when they are heated with P_2S_5 in pyridine. However, our attempts to accomplish this sort of conversion in the case of amines II were unsuccessful. Compound X, which was identified as the 3-thioacetamido derivative from the results of elementary analysis and the IR spectrum, was obtained from Va. Like V, it is converted to IIa upon acid hydrolysis.



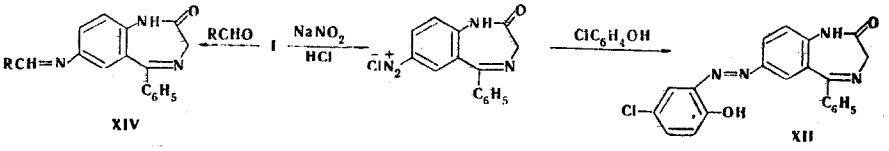
XIII

XI

X

XIII a X = H; b X = *p*-Cl; c X = *p*-Br; d X = *p*-NO_2

The diazotization of II under ordinary conditions leads to the previously described [6] 3-hydroxy derivatives XI. Under the same conditions I forms a diazonium salt that undergoes diazo coupling. The condensation of amines I and II with aldehydes leads to the corresponding aldimines (Table 3).



XIV

XII

XIV a R = C_6H_5; b R = *p*-ClC_6H_4; c R = *p*-BrC_6H_4; d R = *p*-$NO_2C_6H_4$; e R = *m*-$NO_2C_6H_4$; f R = *o*-$NO_2C_6H_4$; g R = *p*-OHC_6H_4; h R = *p*-$NMe_2C_6H_4$; i R = *p*-$(C_2H_5)_2NC_6H_4$; j R = 2-furyl

The condensation of II with benzaldehydes was carried out by refluxing in aprotic solvents in the presence of acid catalysts (zinc chloride and boron trifluoride etherate) or in an alcohol—pyridine medium. Compounds XIV are obtained in satisfactory or good yields by refluxing I with aldehydes in an alcohol—pyridine medium.

We have previously studied the effect of the structure of 1,2-dihydro-3H-1,4-benzodiazepin-2-ones on the half-wave potentials of the polarographic reduction of the azomethine bond of these compounds [7]. The polarographic reduction on a dropping mercury electrode (Table 4) of XIXa-XIVc and XIVh gives two two-electron polarographic waves in each case, one of which is virtually independent of the structure of the compound undergoing reduction, while the second is shifted toward more negative potentials when R = NMe_2 and toward less negative potentials when R = Cl and Br as compared with XIVa. There are four polarographic waves — the first is a four-electron wave and the other three are two-electron waves — on the polarogram of nitro derivatives XIVd. The first two waves on the polarogram of this substance evidently correspond to the successive reduction of the nitro group to a hydroxylamino group and an amino group. As in the case of the other investigated substances of the XIV series, the third and fourth waves correspond to the reduction of the azomethine bonds. Since the polarographic wave found in the region of more negative potantials distinctly experiences the effect of the nature of R, it can be assigned to the reduction of the exocyclic azomethine bond. The polarographic wave at 1115-1130 mV can then be assigned to the reduction of the azomethine bond of the diazepine ring. The half-wave potential of polarographic reduction of IIa is also found near this region (Table 4). Since the potential of the polarographic reduction of the azomethine bond of the diazepine ring of XIV is virtually independent of the nature of R and taking into account the data in [7], it may be concluded that the benzalimine part is removed from conjugation with the benzene ring of the benzodiazepine part of the molecule.

TABLE 4. Half-Wave Potential of the Polarographic Reduction of 7-Aldimino-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-ones

Compound	$-\varphi_{1/2}$, mV
XIVa	1120, 1335
XIVb	1120, 1270
XIVc	1130, 1250
XIVd	430, 680, 1120, 1480
XIVh	1115, 1375
IIa	1180

EXPERIMENTAL

The individuality of the compounds obtained was monitored by thin-layer chromatography on Silufol. The IR spectra of solutions of the compounds in chloroform were recorded with an IKS-14A spectrometer. The polarographic reduction was carried out in a PPT-1 polarograph with a saturated calomel electrode as the reference electrode.

7-Chloro-5-phenyl-3-(3,4,5-trimethoxybenzamido)-1,2-dihydro-3H-1,4-benzodiazepin-2-one (IXb). A 0.28-g (0.0012 mole) sample of 3,4,5-trimethoxybenzoyl chloride was added with stirring to a solution of 0.34 g (0.0012 mole) of IIa in 5 ml of dry pyridine, and the mixture was refluxed for 2 h. The solvent was then removed by vacuum distillation, and the solid residue was treated with a mixture of methylene chloride and water (1:1). The organic layer was separated, dried, and vacuum-evaporated. The solid residue was recrystallized from alcohol to give 0.35 g (63%) of a product with mp 267°C. IR spectrum: 1670-1700 (C=O), 3187-3420 (NH), and 1601 cm^{-1} (C=N).

Compounds IXa and IXc were similarly obtained.

7-Chloro-5-phenyl-3-thioacetamido-1,2-dihydro-3H-1,4-benzodiazepin-2-one (X). A solution of 0.65 g (0.002 mole) of IXa and 0.96 g (0.004 mole) of P_2S_5 in 10 ml of dry pyridine was refluxed with vigorous stirring for 1 h, after which the mixture was cooled and poured into 50 ml of a cold saturated solution of NaCl. The resulting precipitate was removed by filtration, washed with water, and dried to give 0.3 g (48%) with mp 284°C (from benzene). IR spectrum: 1678 (C=O), 3187-3400 (NH), and 1602 cm^{-1} (C=N).

7-Benzalimino-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (XIVa). A 0.4-ml (0.004 mole) sample of benzaldehyde was added to a solution of 0.2 g (0.0008 mole) of I in 1 ml of dry pyridine and 1 ml of absolute methanol, and the mixture was refluxed for 3 h. The alcohol was evaporated in vacuo, and the residue was poured into 10 ml of water. The aqueous mixture was extracted with ether, and the ether extracts were evaporated in vacuo. The residue was recrystallized from alcohol to give 0.16 g (61%) of a product with mp 168-170°C. IR spectrum: 1674 (C=O), 1597-1625 (C=N), and 3188-3400 cm^{-1} (NH).

Compounds XIVb-j were similarly obtained.

7-Chloro-5-phenyl-3-benzalimino-1,2-dihydro-3H-1,4-benzodiazepin-2-one (XIIIa). A mixture of 0.28 g (0.001 mole) of IIa, 0.206 g (0.001 mole) of benzaldehyde, and 25 ml of dry p-xylene was refluxed for 7 h with a Dean–Stark adapter in the presence of a catalytic amount of zinc chloride, after which the xylene was evaporated in vacuo, and the residue was washed with water, sodium carbonate solution, and water and dried to give 0.1 g (29%) of a product with mp 185-187°C (from alcohol). IR spectrum: 1680 (C=O), 1605 (C=N), and 3164-3410 cm^{-1} (NH).

7-Bromo-5-phenyl-3-hydroxy-1,2-dihydro-3H-1,4-benzodiazepin-2-one (XI). A 5% solution of 0.06 g (0.008 mole) of $NaNO_2$ was added dropwise with vigorous stirring to a solution of 0.26 g (0.0008 mole) of IIb in 4 ml of 0.5 N HCl, and the precipitated crystals were removed by filtration to give 0.18 g (70%) of a product with mp 202-203°C (from alcohol).

7-(5-Chloro-2-hydroxyphenyleneazo)-5-phenyl-1,2-dihydro-3H-1,4-benzodiazepin-2-one (XII). A solution of 0.07 g of $NaNO_2$ in 1 ml of water was added with stirring to a cooled (to 0°C) solution of 0.25 g (0.001 mole) of I in 1 ml of HCl, and the mixture was allowed to stand

for 1 h. The resulting diazonium salt was then added with stirring to 0.13 g (0.001 mole) of p-chlorophenol in a saturated solution of Na_2CO_3, and the mixture was allowed to stand for another hour (neutral medium). It was then extracted with CH_2Cl_2, and the extract was evaporated in vacuo to give 0.2 g (54%) of a product with mp 288-290°C (from benzene). Found: C 60.8; H 3.8; N 14.0%. $C_{21}H_{15}ClN_4O_2$. Calculated: C 60.5; H 3.8; N 14.3%. IR spectrum 1675 (C=O), 1610 (C=N), and 3187-3400 cm^{-1} (NH).

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HETEROCYCLIC NITRO COMPOUNDS.

22.* NITRATION OF 1,2,4-TRIAZOLE AND ITS DERIVATIVES WITH NITRONIUM SALTS

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1,2,4-Triazole, 3(5)-R-1,2,4-triazoles (R = CH_3, CL, Br, NO_2), and their N-trimethylsilyl derivatives were nitrated with nitronium salts. The products were N-nitro-1,2,4-triazoles, which split out the nitro group under the influence of acids and undergo rearrangement to 3-nitrotriazoles when they are heated in inert solvents. When R = NO_2, a dinitrotriazole is not formed, and the starting 3-nitro-1,2,4-triazole is recovered.

Attempts to synthesize 3(5)-nitro-1,2,4-triazoles by nitration of triazole derivatives with acidic nitrating agents have been unsuccessful because of the low reactivities of the ring carbon atoms with respect to electrophiles and the additional deactivation of the triazoles when they are protonated in acids [2-4]. The nitration of 1,2,4-triazol-5-one with nitric acid [4-7] constitutes an exception due to disruption of the aromatic ring. The only example of the nonacidic nitration of triazoles is the reaction of 3-phenyl-1,2,4-triazole with acetyl nitrate, which leads to the N-nitro derivatives; the latter then undergoes rearrangement to give the C-nitro compound [8].

We have observed that N-nitro-1,2,4-triazoles (VI-X) are formed in the reaction of 1,2,4-triazole (I) or 3-substituted 1,2,4-triazoles (II-V) with nitronium tetrafluoroborate in anhydrous acetonitrile. Because of their low stabilities, we were able to isolate only the derivatives of triazoles I and II (VI and VII). In the remaining cases the formation of the nitro derivatives can be judged from the PMR spectra of the reaction mixtures and from the

*See [1] for communication 21.

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