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Syntheses of Benzodiazepine Derivatives

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This communication deals with the syntheses of the aza-analogues of benzoheptafulvene. Acetylacetone or benzoylacetone reacted with benzophenone chloride in the presence of sodium ethoxide to form 3-(α-phenylbenzylidene)pentane-2,4-dione (XIVa) or 1-phenyl-2-(α-phenylbenzylidene)butane-1,3-dione (XIVc) respectively. Treatment of *o*-phenylenediamine with XIVa in acetic acid - ethanol resulted in forming 2,4-dimethyl-3-(α-phenylbenzylidene)-3*H*-benzo[*b*]-1,5-diazepine (XVa) which has a 3,6-diaza-4,5-benzoheptafulvene ring skeleton. Similarly, substituted *o*-phenylenediamines reacted with XIVa to give 7-substituted 2,4-dimethyl-3-(α-phenylbenzylidene)-3*H*-benzo[*b*]-1,5-diazepines (XVb)—(XVd). Reaction of XIVa with hydrazine gave only the monohydrazone of XIVa. The ketene dimer reacted with *o*-phenylenediamines to give 4-methyl-2,3-dihydro-2-oxo-1*H*-benzo[*b*]-1,5-diazepines (Xa)—(Xc). However, the condensation of Xa with aldehyde gave an undesirable product.

Although a number of seven membered ring compounds containing nitrogen have been prepared by several workers,[1] aza-analogues of tropone, heptafulvene and fulvene have not been investigated extensively. Only the following are known of the compounds involving such ring systems: 3-hydroxyimino-2,4-dimethyl-3*H*-benzo[*b*]-1,5-diazepine (I),[2] 2,4-diphenyl-3-oxo-3*H*-benzo[*b*]-1,5-diazepine

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[1] A. Yokoo, *Yuki Gosei Kagaku Kyokai Shi*, **24**, 532 (1966).

[2] J. A. Barltrop, C. G. Richard, D. M. Russel and G. Ryback, *J. Chem. Soc.*, **1959**, 1132.

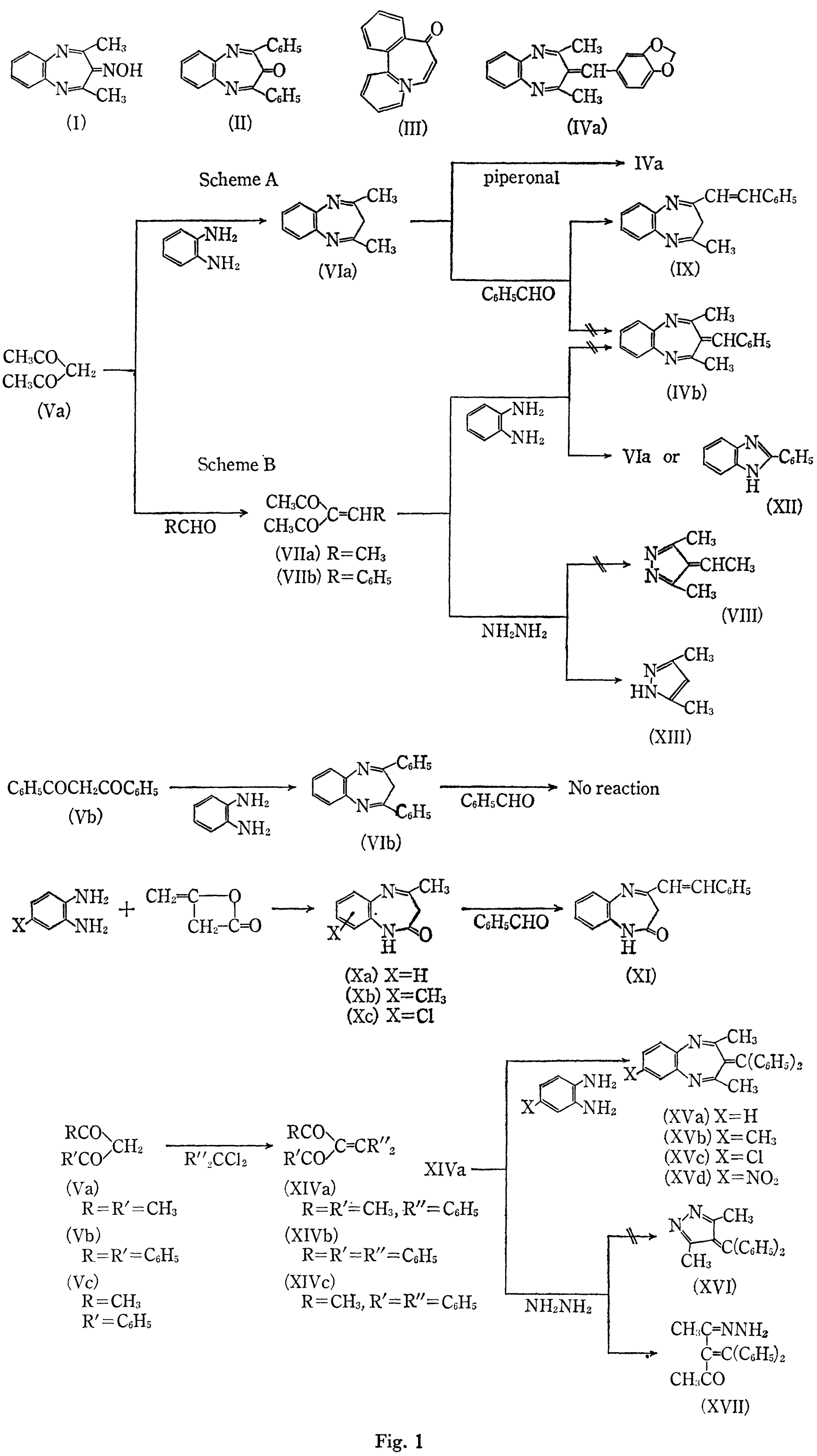
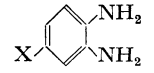

(I)
(II)
(III)
(IVa)
Scheme A
piperonal
IVa
C6H5CHO
(VIa)
(IX)
(IVb)
CH3CO CH2 CH3CO
(Va)
Scheme B
RCHO
CH3CO C=CHR CH3CO
(VIIa) R=CH3
(VIIb) R=C6H5
VIa or
(XII)
NH2NH2
(VIII)
(XIII)
C6H5COCH2COC6H5
(Vb)
(VIb)
C6H5CHO
No reaction
(Xa) X=H
(Xb) X=CH3
(Xc) X=Cl
C6H5CHO
(XI)
RCO CH2 R'CO
R''2CCl2
RCO C=CR''2 R'CO
(Va) R=R'=CH3
(Vb) R=R'=C6H5
(Vc) R=CH3 R'=C6H5
(XIVa) R=R'=CH3, R''=C6H5
(XIVb) R=R'=R''=C6H5
(XIVc) R=CH3, R'=R''=C6H5
XIVa
(XVa) X=H
(XVb) X=CH3
(XVc) X=Cl
(XVd) X=NO2
NH2NH2
(XVI)
CH3C=NNH2 C=C(C6H5)2 CH3CO
(XVII)

Fig. 1

Table 1. Preparation of unsubstituted and substituted 4-methyl-2,3-dihydro-2-oxo-1*H*-benzo[*b*]-1,5-diazepine

		Ketene dimer* g	Time** hr	Solvent (C_6H_6) m*l*	Products					
						Yield %	Mp*** °C	Anal. %		
X	g								Found	Calcd
H	4.3	3.4	3.5	80	Xa	54****	147—148 (lit, 151)		—	—
CH_3	4.9	3.4	4.0	55	Xb	20	174—175	C H N	69.87 6.71 15.05	70.18 6.43 14.88
Cl	5.7	3.4	5.0	60	Xc	42	174—175	C H N Cl	57.84 4.38 13.42 17.04	57.55 4.32 13.43 17.03

* The ketene dimer was dissolved in 10 m*l* of benzene.

** Temperature was maintained at about 45—55°C during the reaction.

*** The products were recrystallized from benzene.

**** The yield was not recorded in literature.

(II),[3] 8-oxo-8*H*-dibenzo[*a*,*c*]azepine (III)[4] and 2,4-dimethyl-3-piperonylidene-3*H*-benzo[*b*]-1,5-diazepine (IVa).[2] In this paper, the syntheses of various aza-analogues of benzoheptafulvenes (XVa)—(XVd) have been described.

The benzodiazepine such as IVa may be synthesized either by scheme A or scheme B as illustrated in Fig. 1. In scheme A, *o*-phenylenediamine is first condensed with *β*-diketones (V) to benzodiazepines (VI) which are then condensed with aldehydes at their 3 position. In scheme B, *β*-diketones are converted to *α*-alkylidene- or arylidene-*β*-diketones (VII) preceding the ring formation and then condensed with *o*-phenylenediamine. Similarly, a compound such as VIII may be prepared by the reaction of hydrazine and VII in accordance with scheme B. Barltrop *et al.*[2] reported that the condensation of VIa with piperonal gave IVa whereas the reaction with benzaldehyde took place at the methyl group in VIa to give the undesirable compound (IX). In our experiment, the diazepine (VIb) which posseses no methyl group in the side chain was allowed to react with benzaldehyde. However, the reaction did not proceed even under various conditions and the starting materials were recovered.

Accordingly, the condensation of 4-methyl-2,3-dihydro-2-oxo-1*H*-benzo[*b*]-1,5-diazepine (Xa) with aldehydes was examined, since the methylene group of Xa appeared to be more reactive than that of VI. Although several procedures for the preparation of Xa are available,[5-7] the method by the reaction of the ketene dimer with *o*-phenylenediamine[5] was found to be the most convenient. Xa and 7- or 8-substituted 4-methyl-2,3-dihydro-2-oxo-1*H*-benzo[*b*]-1,5-diazepines (Xb and Xc) were prepared by the reaction of the ketene dimer with *o*-phenylenediamine, 3,4-diaminotoluene and 3,4-diaminochlorobenzene. Xa reacted with benzaldehyde in the presence of piperidine to give a condensation product. The NMR spectra of the product in $CDCl_3$ exhibited one methylene singlet but no methyl singlet in contrast with those of Xa. Thus the product was assumed to be 4-styryl-2,3-dihydro-2-oxo-1*H*-benzo[*b*]-1,5-diazepine (XI). Similarly, condensation of Xa with other aromatic aldehydes or furfural occurred at the methyl group of Xa.

As we found that the syntheses of the compound of the type IV were unsuccessful by scheme A, a different synthetic approach was investigated following scheme B. *α*-Alkylidene- or arylidene-*β*-diketones (VII) are readily prepared by the condensation of *β*-diketones with aldehydes. Barltrop *et al.*[2] reported that the reaction of 3-benzylidenepentane-2,4-dione (VIIb) with *o*-phenylenediamine yielded 2-phenylbenz[*d*]imidazole (XII) or diazepine (VIa) depending upon the reaction conditions. We examined the reaction of 3-ethylidenepentane-2,4-dione (VIIa) with *o*-phenylenediamine or hydrazine under various conditions. The attempts were also unsuccessful and the product isolated was diazepine (VIa) or dimethylpyrazole (XIII).

Although the reaction of diamines with VII is complicated and may yield a variety of products depending upon the reaction conditions, Pauly[8] reported that the reaction of ethyl *α*-isopropylideneacetoacetate with phenylhydrazine gave 1-phenyl-3-methyl-4-isopropylidene-5-pyrazolone which contains exo double bond. This fact suggests that the

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[3] T. Yonezawa, M. Matsumoto and H. Kato, This Bulletin, **41**, 2543 (1968).

[4] W. Paterson, G. R. Procter, *J. Chem. Soc.*, **1962**, 3468.

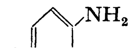
[5] W. Ried and P. Stahlhofen, *Chem. Ber.*, **90**, 825 (1957).

[6] W. A. Sexton, *J. Chem. Soc.*, **1942**, 303.

[7] J. Davoll, *ibid.*, **1960**, 308.

[8] H. Pauly, *Ber.*, **30**, 481 (1897).

TABLE 2. PREPARATION OF UNSUBSTITUTED AND SUBSTITUTED 2,4-DIMETHYL-3-(α-PHENYLBENZYLIDENE)-3*H*-BENZO[*b*]-1,5-DIAZEPINES

 X	g	XIVa g	Time hr	Solvent EtOH m*l*	HOAc m*l*	Products	Yield %	Mp* °C	Anal. %	Found	Calcd
CH_3	2.5	5.3	7	5	2	XVb	40	141—142	C H N	85.65 6.52 8.08	85.68 6.33 7.99
Cl	2.9	5.3	2	10	2	XVc	50	156	C H N Cl	77.94 5.19 7.53 9.59	77.73 5.13 7.56 9.58
NO_2	3.1	5.3	4	5	3	XVd	7	205—206	C H N	75.53 4.98 10.72	75.57 5.02 11.02

* The products were recrystallized from methanol.

β-diketone such as XIV would undergo the ring closure with diamines in the desired manner. Compound XIV is extremely inaccessible as compared with VII because the direct condensation of β-diketones with ketones to form XIV is difficult. However, when acetylacetone (Va), dibenzoylmethane (Vb) and benzoylacetone (Vc) was allowed to react with benzophenone chloride in the presence of sodium ethoxide, 3-(α-phenylbenzylidene)pentane-2,4-dione (XIVa) and 1-phenyl-2-(α-phenylbenzylidene)butane-1,3-dione (XIVc) were obtained. In the case of XIVb the reaction product was a waxy solid and could not be identified owing to difficulties in purification.

When XIVa was heated with *o*-phenylenediamine in ethanol-acetic acid, a crystalline product was obtained. The elementary analysis of the product indicated the empirical formula, $C_{23}H_{20}N_2$ and the NMR spectra showed only two signals, one for phenyl protons (2.8 τ, multiplet, 14H) and the other for methyl protons (8.0 τ, singlet, 6H), while the IR spectra showed no NH stretching band. Thus the product was identified as 2,4-dimethyl-3-(α-phenylbenzylidene)-3*H*-benzo[*b*]-1,5-diazepine (XVa) which has a 3,6-diaza-4,5-benzoheptafulvene ring skeleton. Similarly, treatment of XIVa with 3,4-diaminotoluene, 3,4-diaminochlorobenzene and 3,4-diaminonitrobenzene gave the corresponding 7-substituted benzodiazepines (XVb)—(XVd). The reaction of XIVb with *o*-phenylenediamine was also examined but no identified product was obtained. On the other hand, the reaction of XIVa with hydrazine in acetic acid gave high melting white crystals. Its analytical values agreed better with the calculated values for XVII than those for diazafulvene (XVI) and the IR spectra clearly exhibited a broad NH stretching band. Therefore, the product is assumed to be 4-hydrazono-3-(α-phenylbenzylidene)pentan-2-one.

Experimental

4-Methyl-2,3-dihydro-2-oxo-1*H*-benzo[*b*]-1,5-diazepine (Xa). This compound was prepared by the method given in literature.[5]

4,7(or 8)-dimethyl-2,3-dihydro-2-oxo-1*H*-benzo[*b*]-1,5-diazepine (Xb) and 7(or 8)-chloro-4-methyl-2,3-dihydro-2-oxo-1*H*-benzo[*b*]-1,5-diazepine (Xc) were prepared similarly by the reaction of the ketene dimer with 3,4-diaminotoluene and 3,4-diaminochlorobenzene. The results are summarized in Table 1.

4-Styryl-2,3-dihydro-2-oxo-1*H*-benzo[*b*]-1,5-diazepine (XI). A solution of 3.5 g of Xa, 2.0 g of benzaldehyde and three drops of piperidine in 15 m*l* of benzene was refluxed for 15 hr. After cooling, precipitated product was filtered, recrystallized from ethanol and 1.1 g of XI was obtained; yield 21.2%, yellow needles, mp 218—219°C.

Found: C, 78.10; H, 5.17; N, 10.57%. Calcd for $C_{17}H_{14}ON_2$: C, 77.84; H, 5.38; N, 10.68%.

3-(α-Phenylbenzylidene)pentane-2,4-dione (XIVa). Into a solution of sodium ethoxide, prepared from 15.3 g of sodium and 300 m*l* of ethanol, 66.7 g of acetylacetone was added. The mixture was then heated under reflux and 79 g of benzophenone chloride was added over a period of 1 hr. After addition of the chloride, the mixture was refluxed a further 2 hr. Carbon dioxide was passed through the cooled reaction mixture for 10 min and the precipitate was filtered and washed with ethanol repeatedly. The filtrate was steam-distilled to remove most of the ethanol and excess of acetylacetone. An oily product separated in the residue was extracted with ether and the extract was dried over anhydrous sodium sulphate. After the ether was removed, the residue was distilled and a fraction boiling at 165—181°C/7 mmHg was collected. The distillate solidified immediately in the receiver and was recrystallized from ligroin to give 34.4 g (39.1%) of XIVa, colorless needles, mp 120—121°C.

Found: C, 81.52; H, 6.23%. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10%.

1-Phenyl-2-(α-phenylbenzylidene)butane-1,3-dione (XIVc). As in the preceding procedure, 23.2 g of benzophenone chloride was treated with sodium benzoylacetonate, prepared from 4.6 g of sodium and 32.4 g of benzoylacetone in 100 m*l* of ethanol. After the reaction was over, carbon dioxide was passed through the reaction mixture and the precipitate was filtered and washed with 10 m*l* of ethanol. The filtrate was cooled in an ice-salt bath and the crystalline product separated was collected and recrystallized from ethanol. XIVc was obtained as light yellow needles, mp 126°C, yield 4.7 g (14.7%).

Found: C, 84.78; H, 5.50%. Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56%.

2,4-Dimethyl-3-(*α*-phenylbenzylidene)-3*H*-benzo-[*b*]-1,5-diazepine (XVa). A solution of 2.6 g of XIVa and 1.1 g of *o*-phenylenediamine in 10 m*l* of ethanol containing 1 m*l* of acetic acid was refluxed for 3 hr. After cooling, the product precipitated was filtered and recrystallized from methanol. XVa was obtained as white needles, mp 156—157°C, yield 2.1 g (62.5%).

Found: C, 85.37; H, 5.67; N, 8.53%. Calcd for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33%.

Similarly, 7-substituted 2,4-dimethyl-3-(α-phenylbenzylidene)-3*H*-benzo[*b*]-1,5-diazepines (XVb)—(XVd) were prepared by the reaction of XIVa with 3,4-diaminotoluene, 3,4-diaminochlorobenzene and 3,4-diaminonitrobenzene respectively. The results are summarized in Table 2.

4-Hydrazono-3-(*α*-phenylbenzylidene)pentan-2-one (XVII). A mixture of 2.6 g of XIVa, 0.5 g of hydrazine hydrate and 6 m*l* of acetic acid was refluxed for 1 hr. After cooling, 100 m*l* of water was added and the mixture was allowed to stand for 2—3 hr. Precipitated product was filtered and recrystallized from methanol to give 1.6 g of XVII, mp 217—219°C.

Found: C, 77.71; H, 6.20; N, 9.99%. Calcd for $C_{18}H_{18}ON_2$: C, 77.67: H, 6.52; N, 10.07%.

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