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Syntheses of Benzo[*e*]-1,3,4-triazepine Derivatives from 2-Aminobenzophenones[1)]

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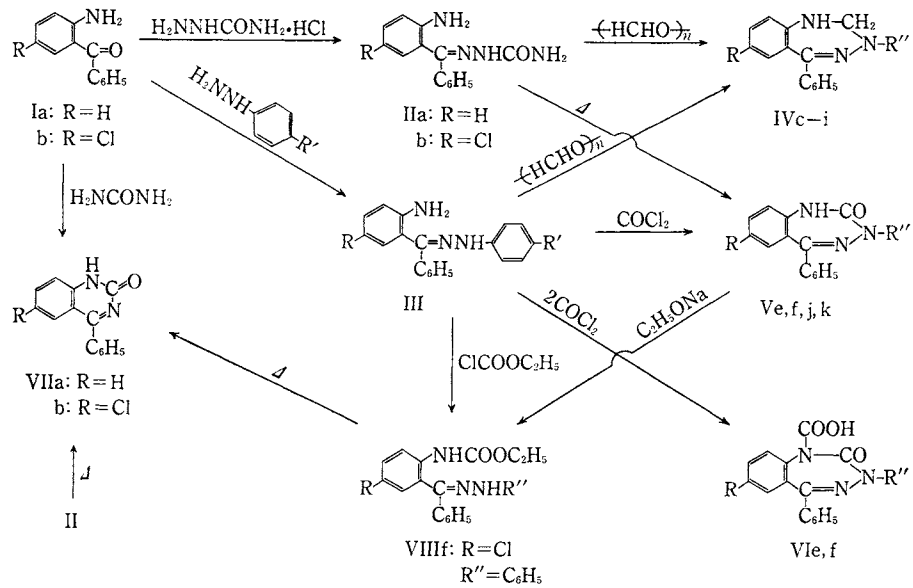
2-Aminobenzophenone semicarbazones (II) or 2-aminobenzophenone phenylhydrazones (III) were cyclized to 3,7-disubstituted 5-phenyl-2,3-dihydro-1*H*-benzo[*e*]-1,3,4-triazepines (IV) by treating them with paraformaldehyde. On the other hand, 3,7-disubstituted 2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*]-1,3,4-triazepines (V) were prepared by the fusion of II at 190—195°C or by the treatment of III with phosgene. In the latter reactions, 1-carboxy derivatives (VI) of V were obtained by using two equimolar amounts of phosgene. Vf was treated with sodium ethoxide to give a ring-cleavage product, 5-chloro-2-ethoxycarbonylaminobenzophenone phenylhydrazone (VIIIf), which was then fused to afford 6-chloro-1,2-dihydro-2-oxo-4-phenylquinazoline (VIIb).

Although some 7-substituted 2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*]-1,3,4-triazepines have been prepared by Sulkowski and Childress[2,3)] in recent years, the syntheses of 3,7-disubstituted benzo[*e*]-1,3,4-triazepines and 2-oxo-benzo[*e*]-1,3,4-triazepines have never been reported. Now, this paper will report the syntheses of several new benzo[*e*]-1,3,4-triazepines and 2-oxo-benzo[*e*]-1,3,4-triazepines from 2-aminobenzophenones (I), and will describe their properties.

Compounds Ia and Ib[4,5)] were treated in the customary way with semicarbazide hydrochloride



c-k: R and R″ are shown in Table 1

Scheme 1

1) Part VII of "*o*-Aminobenzophenone Derivatives." This paper was presented at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, April, 1968. Part VI: Y. Toi, K. Isagawa and Y. Fushizaki, *Nippon Kagaku Zasshi*, **90**, 1047 (1969).

2) T. S. Sulkowski and S. J. Childress, *J. Med. Chem.*, **7**, 386 (1964).

3) T. S. Sulkowski and S. J. Childress, U. S. 3176008; *Chem. Abstr.*, **62**, 16284 (1965).

4) L. H. Sternbach, E. Reeder, O. Keller and W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961).

5) H. J. Scheifele, Jr., and D. F. DeTar, "Organic Syntheses," Coll. Vol. IV, p. 34 (1962).

or phenylhydrazines to give semicarbazones (IIa and IIb) or phenylhydrazones (III). 3,7-Disubstituted 5-phenyl-2,3-dihydro-1*H*-benzo[*e*]-1,3,4-triazepines and 3,7-disubstituted 2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*]-1,3,4-triazepines were prepared according to the methods outlined below (Scheme 1).

The first method employed was the condensation of II or III with paraformaldehyde in refluxing xylene. The compounds IV shown in Table 1 were obtained by this method.

The second method was the intramolecular condensation. IIa and IIb gave 2-oxo-benzo[*e*]-1,3,4-triazepines (Vj and Vk respectively) on fusion at 190—195°C. The fusion of IIa and IIb at 230—240°C, however, did not give the 2-oxo-benzo[*e*]-1,3,4-triazepines, but instead produced the corresponding 1,2-dihydro-2-oxo-4-phenylquinazolines (VIIa) and (VIIb), which were identified by their preparation from Ia or Ib and urea.[6]

The third convenient approach was the treatment of III (R=R′=H, or R=Cl, R′=H) with phosgene according to the method of Sulkowski.[2] In this reaction, it was found that a small amount of 1-carboxy-3,5-diphenyl-2-oxo-2,3-dihydro-1*H*-benzo[*e*]-1,3,4-triazepine (VIe) along with a desired 2-oxo-benzo[*e*]-1,3,4-triazepine Ve, and the 1-carboxy-7-chloro derivative (VIf), along with Vf, were formed. By using two equimolar amounts of phosgene, the yields of VIe and VIf were increased to 16% and 30% respectively.

Several new compounds prepared in the course of this work, are summarized in Table 1.

Vf brought about a ring-cleavage reaction in the presence of sodium ethoxide to afford 5-chloro-2-ethoxycarbonylaminobenzophenone phen-

Table 1. Benzo[*e*]-1,3,4-triazepines and 2-oxo-benzo[*e*]-1,3,4-triazepines

		Compound R	Compound R″	Yield (%)	Mp (°C)	Elementary analysis (%) Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
IV	c	H	$CONH_2$	15	209—210	67.65	5.30	21.04	67.65	5.39	20.86
	d	Cl	$CONH_2$	13	217—218	59.91	4.36	18.63	60.20	4.51	18.36
	e	H	C_6H_5	27	180—181	80.24	5.72	14.04	80.15	5.64	14.03
	f	Cl	C_6H_5	24	168—169	71.96	4.83	12.59	72.27	4.79	12.72
	g	Cl	*p*-$CH_3C_6H_4$	22	141—142	72.51	5.22	12.08	72.77	5.34	11.82
	h	Cl	*p*-ClC_6H_4	34	137—138	65.23	4.11	11.41	64.99	4.22	11.19
	i	Cl	*p*-$COOC_2H_5C_6H_4$	23	181—182	68.06	4.97	10.35	67.78	4.88	10.19
V	e	H	C_6H_5	14	207—208	76.66	4.83	13.41	76.36	4.80	13.13
	f	Cl	C_6H_5	40	243—244	69.07	4.06	12.08	69.00	4.08	12.03
	j	H	H	20	230—231[a]	70.87	4.67	17.71	70.60	4.80	17.52
	k	Cl	H	25	235—237[b]	61.89	3.71	15.47	61.99	3.90	15.74
VI	e	H	C_6H_5	16	141—142	70.58	4.23	11.76	70.47	4.21	11.63
	f	Cl	C_6H_5	30	172—173	64.38	3.60	10.72	64.66	3.79	10.42

a) Lit,[2] mp 238°C.
b) Lit,[2] mp 246—248°C.

Table 2. Spectroscopic data for 2-oxo-benzo[*e*]-1,3,4-triazepines

Compounds		UV[a] (mμ) λ_{max} ($\varepsilon\times10^{-4}$)			IR[b] (cm^{-1}) C=O	IR[b] (cm^{-1}) C=O	NMR[c] δ (ppm) NH	NMR[c] δ (ppm) COOH	NMR[c] δ (ppm) Arom H
V	e	224[s](2.54)	246[s](1.99)	300 (0.39)	1680	—	9.52[b]	—	7.10—7.72[m]
	f	227 (3.51)	248[s](2.06)	309 (0.42)	1690	—	9.72[b]	—	7.05—7.83[m]
	j	222[s](3.10)	247[s](1.58)	294 (0.71)	1700	—	9.02[b]	—	6.94—7.86[m]
	k	224 (4.45)	250[s](2.42)	302 (0.90)	1700	—	9.10[b]	—	6.91—7.79[m]
VI	e	250 (3.21)	356 (0.61)		1650	1785	—	11.22[b]	7.10—8.46[m]
	f	250 (3.68)	371 (0.56)		1650	1785	—	11.06[b]	7.28—8.48[m]

a) Measured in 99% EtOH. s: shoulder
b) Measured in $CHCl_3$ (0.002 mol/*l*) for Ve, Vj, Vk, VIe and VIf: measured in KBr disk for Vf.
c) Measured in $CDCl_3$-DMSO-d_6 (1:2) for Ve, Vf, Vj and Vk: measured in $CDCl_3$ for VIe and VIf, using tetramethylsilane as the internal standard. b: broad, m: multiplet.

6) T. S. Sulkowski and S. J. Childress, *J. Org. Chem.*, **27**, 4424 (1962).

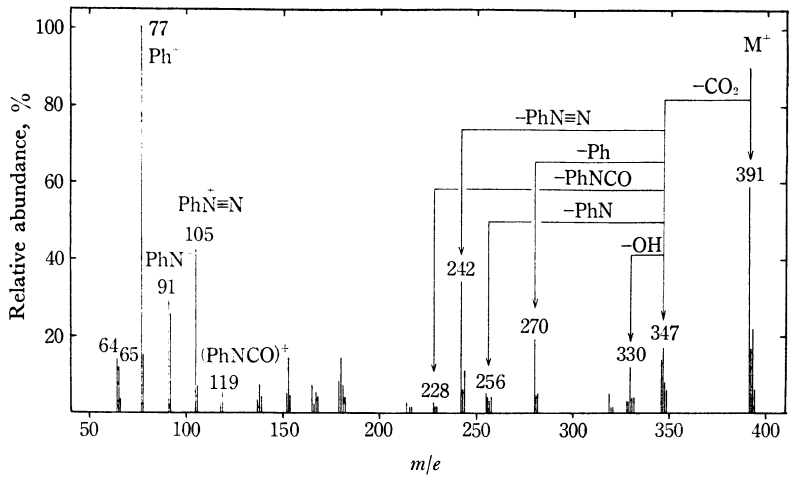


Fig. 1. Mass spectrum of VIf.

ylhydrazone (VIIIf), which was also prepared by the reaction of III (R=Cl, R'=H) with ethyl chlorocarbonate. VIIIf was heated at 170—175°C to give VIIb.

The UV, IR, and NMR data for the 2-oxo-benzo[e]-1,3,4-triazepine derivatives are shown in Table 2. By comparing the UV spectra of Ve and Vf with those of VIe and VIf, it is found that the absorption bands of VIe and VIf are situated in a region of wavelength longer than those of the corresponding Ve and Vf. The IR spectra (chloroform) of VIe and VIf showed the bands at 1785 cm^{-1} and 1650 cm^{-1} due to two carbonyl groups; the lower-frequency band can be assigned to the carbonyl group of lactam. The facts that the lactam C=O groups of both VIe and VIf appear at a lower frequency than those of Ve and Vf (KBr disk), and that the carboxylic C=O groups of VIe and VIf exist in a region of higher frequency,*1 suggest the presence of strong intramolecular hydrogen bonds in VIe and VIf. The mass spectrum of VIf is shown in Fig. 1, where the molecular ion peak is observed at *m/e* 391 (relative isotope ratio, 35.7%) and where the fragment at *m/e* 347 (relative isotop ratio, 33.7%), which corresponds to 7-chloro-2-oxo-benzo[e]-1,3,4-triazepine Vf or 7-chloro-3,5-diphenyl-2-hydroxy-benzo[e]-1,3,4-triazepine, is formed by the loss of CO_2 from the molecular ion. Furthermore, the relative abundance of the molecular ion peak is quite strong, so the molecular ion is probably more stable.

*1 Mori and his co-workers[7] discussed the intramolecular hydrogen bonds of α-hydroxy carboxylic and *o*-hydroxy benzoic acids by measuring their infrared carbonyl stretching absorption spectra. They reported that *trans*-carbonyl C=O groups of salicylic and mandelic acids could be expected at 1750 cm^{-1} and 1785 cm^{-1} respectively.

7) N. Mori, Y. Asano, T. Irie and Y. Tsuzuki, This Bulletin, **42**, 482 (1969).

Experimental

All the melting points are uncorrected. The infrared spectra were recorded with a Hitachi EPI-S2 infrared spectrophotometer. The ultraviolet spectra were obtained using a Hitachi EPS-2U recording spectrophotometer. The NMR spectra were determined on a Hitachi R-20 spectrometer, while the mass spectrum was determined with a Hitachi Model RMU-6D spectrometer.

General Method for the Preparation of Benzo-[e]-1,3,4-triazepines (IV). *i*) A solution of equimolar amounts of II and paraformaldehyde (5 mmol each) in 50 m*l* of dry xylene was refluxed for 6 hr. The reaction mixture was concentrated *in vacuo*. The residual oil was taken up in 50 m*l* of ether, the insoluble material was removed by filtration, the filtrate was evaporated to dryness *in vacuo*, and the residue was purified by recrystallization.

3-Carbamoyl-5-phenyl-2,3-dihydro-1H-benzo[e]-1,3,4-triazepine (IVc). Pale yellow needles. UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$): 229 (3.24), 299(0.88); IR(KBr): 3490, 3350, 1705 cm^{-1}.

3-Carbamoyl-7-chloro-5-phenyl-2,3-dihydro-1H-benzo[e]-1,3,4-triazepine (IVd). Pale yellow needles. UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$): 235 (2.89), 292(1.06); IR(KBr): 3430, 3280, 1695 cm^{-1}.

ii) A solution of equimolar amounts of III and paraformaldehyde (5 mmol each) in 50 m*l* of dry xylene was refluxed for 6 hr. After the solvent had then been removed, the residue was dissolved in benzene and chromatographed on silica gel with the same solvent. The first eluate (about 70 m*l*) was concentrated *in vacuo*, the residual oil was solidified by adding *n*-hexane, and the resulting crystals were purified by recrystallization.

3,5-Diphenyl-2,3-dihydro-1H-benzo[e]-1,3,4-triazepine (IVe). Yellow needles. UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$): 230(3.41), 331(1.05); IR(KBr): 3430 cm^{-1}: NMR ($CDCl_3$): δ 6.62—7.60 (m, 14H, aromatic protons), δ 5.14(s, 1H, NH), δ 4.97 ppm(s, 2H, CH_2).

7-Chloro-3,5-diphenyl-2,3-dihydro-1H-benzo[e]-1,3,4-triazepine (IVf). Yellow prisms. UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$): 233(2.95), 256^{s}(2.34), 333(0.95); IR(KBr): 3410, 1600

cm^{-1}; NMR($CDCl_3$): δ 6.70—7.69(m, 13H, aromatic protons), δ 5.05(b, 1H, NH), δ 4.92 ppm (s, 2H, CH_2).

7-Chloro-5-phenyl-3-(4-tolyl)-2,3-dihydro-1H-benzo[e]-1,3,4-triazepine (IVg). Yellow needles. UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$): 234(2.54), 255^s(2.21), 338(0.77); IR(KBr): 3400, 1610 cm^{-1}; NMR($CDCl_3$): δ 6.68—7.72(m, 12H, aromatic protons), δ 4.95(b, 1H, NH), δ 4.92(s, 2H, CH_2), δ 2.31 ppm (s, 3H, CH_3).

7-Chloro-3-(4-chlorophenyl)-5-phenyl-2,3-dihydro-1H-benzo-[e]-1,3,4-triazepine (IVh). Yellow needles. UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$): 232(2.06), 265(1.77), 335(0.69); IR (KBr): 3400, 1590 cm^{-1}; NMR ($CDCl_3$): δ 6.70—7.76 (m, 12H, aromatic protons), δ 5.03(b, 1H, NH), δ 4.87 ppm (s, 2H, CH_2).

7-Chloro-3-(4-ethoxycarbonylphenyl)-5-phenyl-2,3-dihydro-1H-benzo[e]-1,3,4-triazepine (IVi). Yellow needles. UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$): 236.5(1.72), 269(1.01), 336.5(1.21); IR(KBr): 3390, 1690, 1610 cm^{-1}; NMR($CDCl_3$): δ 6.72—8.12(m, 12H, aromatic protons), δ 5.13(b, 1H, NH), δ 4.99(s, 2H, CH_2), δ 4.35(q, 2H, CH_2), δ 1.38 ppm (t, 3H, CH_3).

3,5-Diphenyl-2-oxo-2,3-dihydro-1*H*-benzo[*e*]-1,3,4-triazepine (Ve). To a solution of 1.44 g (5 mmol) of III (R=R'=H) and 2 m*l* of triethylamine in 20 m*l* of benzene, a solution of 20 m*l* of benzene containing 0.50 g of phosgene (5 mmol) was stirred in, drop by drop, at 5—10°C. After having been stirred at room temperature for 2 hr, the reaction mixture was poured into water to remove the triethylamine hydrochloride. The crude product was collected by filtration; subsequent recrystallization from acetone afforded 0.20 g of Ve as yellow prisms.

A small amount of the 1-carboxy derivative (VIe) was obtained from the benzene solution by the same manner as was used in the preparation of VIe (described below).

7-Chloro-3,5-diphenyl-2-oxo-2,3-dihydro-1*H*-benzo[*e*]-1,3,4-triazepine (Vf). This compound was prepared by the same procedure as has been described for the preparation of Ve. 1.61 g (5 mmol) of III (R=Cl, R'=H) and 0.50 g of phosgene gave 0.69 g of Vf as yellow needles.

2-Oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*]-1,3,4-triazepine (Vj). IIa (1.27 g, 5 mmol) was heated to 190—195°C for 1 hr. After cooling to room temperature, the resulting dark solid was shaken with 50 m*l* of ethanol, the insoluble material was removed, and the filtrate was taken to dryness *in vacuo*. The residue was washed with 30 m*l* of methylene chloride and recrystallized from ethanol to afford 0.24 g of Vj as pale yellow needles.

7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo-[*e*]-1,3,4-triazepine (Vk). IIb (1.44 g, 5 mmol) was worked up according to the procedure described for the preparation of Vj. Recrystallization from ethanol afforded 0.34 g of Vk as yellow needles.

1-Carboxy-3,5-diphenyl-2-oxo-2,3-dihydro-1*H*-benzo[*e*]-1,3,4-triazepine (VIe). To a solution of 1.44 g (5 mmol) of III (R=R'=H) in 12 m*l* of benzene containing 2 m*l* of triethylamine, 1.00 g (10 mmol) of phosgene in 20 m*l* of benzene was stirred in, drop by drop, at 5—10°C, and then the resulting solution was stirred at room temperature for an additional 2 hr. After the reaction mixture had then been washed with water and dried over anhydrous magnesium sulfate, the benzene was removed and the residue was recrystallized from a mixture of ethanol and benzene to afford 0.28 g of VIe as yellow needles.

1-Carboxy-7-chloro-2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*]-1,3,4-triazepine (VIf). This compound was prepared by the same procedure as has been described for the preparation of VIe. 1.61 g (5 mmol) of III (R=Cl, R'=H) and 1.00 g (10 mmol) of phosgene gave 0.59 g of VIf as yellow needles.

1,2-Dihydro-2-oxo-4-phenylquinazoline (VIIa). IIa (0.76 g, 3 mmol) was fused at 230—240°C for 3 hr. After cooling to room temperature, the resulting solid was shaken with 50 m*l* of warm ethanol, the insoluble part was removed by filtration, and the yellow solid obtained by the evaporation of the solvent from the filtrate was recrystallized from a mixture of ethyl acetate and ethanol to afford 0.37 g of VIIa as pale yellow prisms; mp 243—245°C; yield 55%.

Found: C, 75.48; H, 4.67; N, 12.83%.

The product was identified by means of mixed-melting-point measurements and by a comparison of its UV and IR spectra with those of the sample obtained from the reaction of Ia with urea.[6]

6-Chloro-1,2-dihydro-2-oxo-4-phenylquinazoline (VIIb). 3-mmol portions of IIb and VIIIf were fused at 230—240°C and 170—175°C respectively. The resulting solid was worked up as has been described above for VIIa and recrystallized from a mixture of ethyl acetate and ethanol to afford VIIb as colorless needles; mp 256—258°C; yields, 0.28 g (36%) and 0.24 g (31%) respectively.

These products were identified by means of mixed-melting-point measurements and by a comparison of their UV and IR spectra with those of the sample obtained from the reaction of Ib with urea.

5-Chloro-2-ethoxycarbonylaminobenzophenone Phenylhydrazone (VIIIf). *i) From Vf.* Into a solution of 0.70 g (2 mmol) of Vf in 150 m*l* of ethanol, a solution of 10 m*l* of ethanol containing 50 mg (22 mmol) of sodium metal was added. After the solution had then been refluxed for 6 hr, the solvent was removed; the residual oil was solidified by adding a small amount of ethanol. The crude crystals were recrystallized from ethanol to afford 0.49 g (62%) of VIIIf as pale yellow needles; mp 174—175°C. UV λ_{max}^{EtOH} mμ ($\varepsilon\times10^{-4}$): 238(2.10), 300(0.87); IR(KBr): 3300, 3410, 1735, 1600 cm^{-1}; NMR ($CDCl_3$): δ 6.69—8.53(m, 13H, aromatic protons), δ 11.62(s, 1H, NH), δ 4.28(q, 2H, CH_2), δ 1.45 ppm(t, 3H, CH_3).

Found: C, 67.08; H, 5.13; N, 10.58%. Calcd for $C_{22}H_{20}N_3O_2Cl$: C, 67.09; H, 5.12; N, 10.67%.

ii) From III (R=Cl, R'=H). Into a solution of 1.61 g (5 mmol) of III (R=Cl, R'=H) in 30 m*l* of dry benzene containing 1 m*l* of triethylamine, a solution of 0.54 g (5 mmol) of ethyl chlorocarbonate in 20 m*l* of dry benzene was stirred in, drop by drop, at room temperature over a 30-min period. After the solution had been refluxed for 6 hr and cooled at room temperature, a benzene-insoluble solid was removed by filtration. The brownish-yellow oil which was obtained by the evaporation of the solvent from the filtrate was solidified by adding a small amount of ethanol. The crude crystals were recrystallized from ethanol to afford 1.16 g (59%) of VIIIf as pale yellow needles; mp 170—172°C.

The product was identified by means of mixed-melting-point measurements and by a comparison of its IR and NMR spectra with those of the above sample.