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Benzodiazepines. I. Syntheses of 4-Phenyl-1,4-benzodiazepine-2, 5-dione Derivatives

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Since Sternbach and Reeder[2] reported the ring enlargement reaction that led 2-methylamino-5-phenyl-7-chloro-3H-1,4-benzodiazepine 4-oxide by treating 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide, various kinds of 5-phenyl-1,4-benzodiazepine derivatives have been published. However, few reports on the benzodiazepine derivatives substituted a phenyl group in the other position of the benzodiazepine ring, for example 4-phenyl substituted benzodiazepine derivatives, have been reported up to the present.

These 4-phenyl-1H-3,4-dihydro-1,4-benzodiazepine-2,5-dione derivatives were prepared from corresponding *o*-(chloroacetamido)benzanilides by us,[3] and then Lee[4,5] reported later the syntheses of these benzodiazepine-2,5-dione derivatives by the same method.

While, J. Krapcho[6] was found that 4-phenyl-1H-3,4-dihydro-1,4-benzodiazepine-2,5-diones could be yielded by reducing N-(*o*-nitrobenzoyl)-N-phenylglycine with 5% palladium carbon.

In this paper, 4-phenyl-1H-3,4-dihydro-1,4-benzodiazepine-2,5-dione derivative are prepared by following processes.

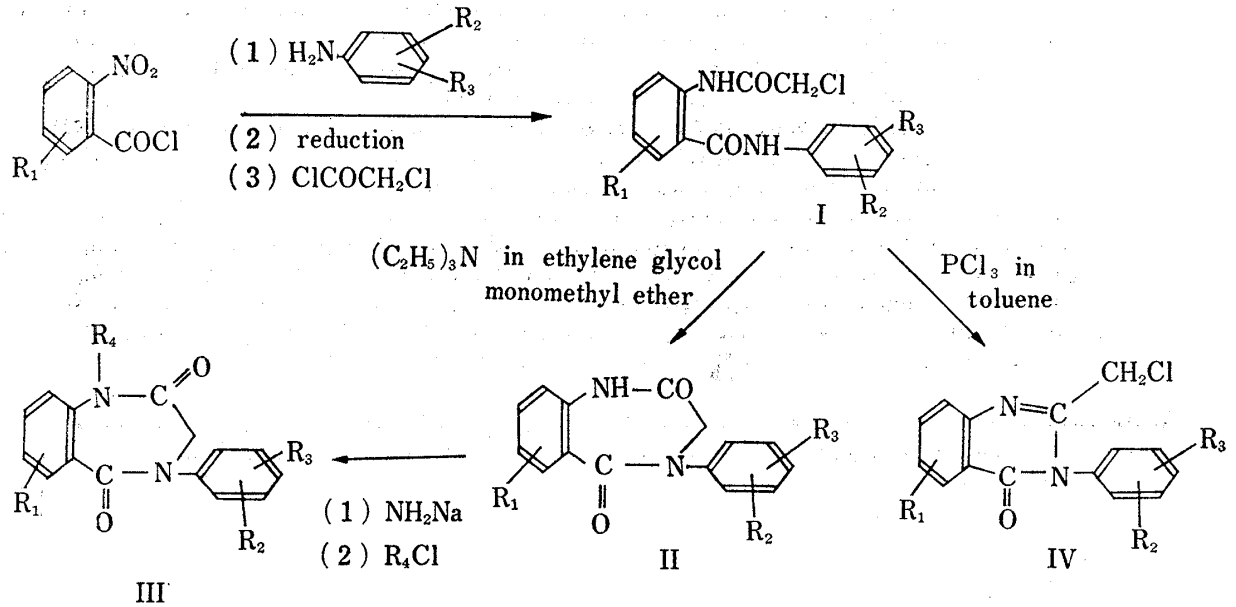
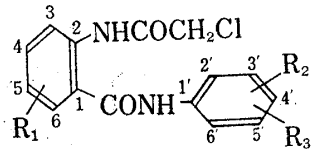


Chart 1

1) Location: *278, Kasugade-cho, Konohana-ku, Osaka.*
2) L.H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 111 (1961).
3) H. Yamamoto, S. Kitagawa and S. Sakai, Japan. Patent Appl. 38-38381 (1963), France Patent 1491502 (1965).
4) Chauk-Man Lee, *J. Heterocycl. Chem.*, **1**, 235 (1964).
5) Chauk-Man Lee, Japan. Patent Appl. 40-58505 (1965).
6) J. Krapcho, U.S. Patent 3173912.

TABLE I.

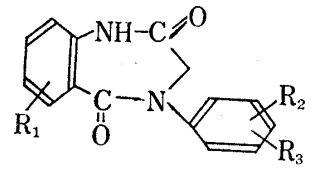


I

Compd. No.	Chemical structure R_1	R_2	R_3	Recryst. solv.	mp[a] (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
I-1	H	H	H	acetone–H_2O	188—189	$C_{15}H_{13}O_2N_2Cl$	62.40	4.54	9.70	62.66	4.41	9.56
I-2	H	4′-Cl	H	MeOH–H_2O	180—181	$C_{15}H_{12}O_2N_2Cl_2$	55.75	3.74	8.67	55.97	3.69	8.49
I-3	H	3′-Cl	H	MeOH–H_2O	169—170	$C_{15}H_{12}O_2N_2Cl_2$	55.75	3.74	8.67	55.61	3.62	8.43
I-4	H	2′-CH_3	H	acetone–H_2O	179—180	$C_{16}H_{15}O_2N_2Cl$	63.47	4.99	9.25	63.63	4.80	9.11
I-5	H	4′-OCH	H	MeOH–H_2O	190—191	$C_{16}H_{15}O_3N_2Cl$	60.29	4.77	8.79	60.24	4.70	8.72
I-6	H	2′-CH_3	3′-Cl	EtOH–H_2O	196—197	$C_{16}H_{14}O_2N_2Cl_2$	56.99	4.18	8.31	57.02	4.16	8.17
I-7	H	2′-CH_3	4′-Cl	acetone–H_2O	173—174	$C_{16}H_{14}O_2N_2Cl_2$	56.99	4.18	8.31	57.16	3.85	8.43
I-8	H	4′-CH_3	H	MeOH	195	$C_{16}H_{15}O_2N_2Cl$	63.47	4.99	9.25	63.66	4.86	9.11
I-9	6-Cl	4′-Cl	H	MeOH–H_2O	202—203	$C_{15}H_{11}O_2N_2Cl_3$	50.38	3.10	7.83	50.42	3.42	7.81
I-10	6-Cl	4′-Br	H	MeOH	210—211	$C_{15}H_{11}O_2N_2Cl_2Br$	—	—	6.97	—	—	7.11
I-11	6-Cl	4′-OCH_3	H	MeOH	213	$C_{16}H_{14}O_3N_2Cl_2$	—	—	7.93	—	—	8.10
I-12	4-Cl	4′-OCH_3	H	dioxane–H_2O	207	$C_{16}H_{14}O_3N_2Cl_2$	54.41	4.00	7.93	54.70	4.20	7.49
I-13	4-Cl	2′-CH_3	3′-Cl	dioxane–H_2O	221—222	$C_{16}H_{13}O_2N_2Cl_3$	51.71	3.53	7.54	52.21	3.79	7.46
I-14	6-Cl	2′-CH_3	3′-Cl	dioxane–H_2O	227	$C_{16}H_{13}O_2N_2Cl_3$	51.71	3.53	7.54	52.21	3.79	7.46
I-15	4-Cl	2′-CH_3	4′-Cl	dioxane–H_2O	222	$C_{16}H_{13}O_2N_2Cl_3$	51.71	3.53	7.54	52.00	3.80	7.53
I-16	6-Cl	2′-CH_3	4′-Cl	MeOH	217—218	$C_{16}H_{13}O_2N_2Cl_3$	51.71	3.53	7.54	51.93	3.71	7.37

a) uncorrected

TABLE II.

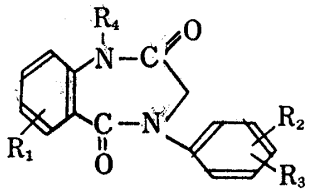


II

Compd. No.	Chemical structure R_1	R_2	R_3	Recryst. solv.	mp[a] (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
II-1	H	H	H	acetone	208—209	57	$C_{15}H_{12}O_2N_2$	71.41	4.80	11.11	71.04	5.03	11.08
II-2	H	4′-Cl	H	MeOH	195—197	76	$C_{15}H_{11}O_2N_2Cl$	62.84	3.87	9.77	63.00	3.78	9.66
II-3	H	3′-Cl	H	EtOH–H_2O	176—177	89	$C_{15}H_{11}O_2N_2Cl$	62.84	3.87	9.77	62.82	3.94	9.67
II-4	H	2′-CH_3	H	MeOH	245—246	66	$C_{16}H_{14}O_2N_2$	—	—	10.52	—	—	10.53
II-5	H	4′-OCH_3	H	MeOH	236—237	66	$C_{16}H_{14}O_3N_2$	—	—	9.92	—	—	9.78
II-6	H	2′-CH_3	3′-Cl	MeOH	176—178	82	$C_{16}H_{14}O_2N_2Cl$	63.90	4.36	9.32	64.08	4.57	8.88
II-7	H	2′-CH_3	4′-Cl	dioxane	193—194	57	$C_{16}H_{14}O_2N_2Cl$	—	—	9.32	—	—	9.26
II-8	H	4′-CH_3	H	MeOH	247—248	67	$C_{16}H_{14}O_2N_2$	—	—	10.52	—	—	10.36
II-9	6-Cl	4′-Cl	H	MeOH	215	—	$C_{15}H_{10}O_2N_2Cl_2$	—	—	8.72	—	—	8.52
II-10	6-Cl	4′-Br	H	MeOH	221—223	55	$C_{15}H_{10}O_2N_2BrCl$	49.27	2.76	—	49.43	3.12	—
II-11	6-Cl	4′-OCH_3	H	MeOH	208—209	40	$C_{16}H_{13}O_3N_2Cl$	60.67	4.14	8.84	60.84	4.56	9.03
II-12	8-Cl	4′-OCH_3	H	MeOH	298	75	$C_{16}H_{13}O_3N_2Cl$	—	—	8.84	—	—	9.12
II-13	8-Cl	2′-CH_3	3′-Cl	MeOH	160—161	50	$C_{16}H_{12}O_2N_2Cl_2$	—	—	8.36	—	—	8.30
II-14	6-Cl	2′-CH_3	3′-Cl	MeOH	163—164	—	$C_{16}H_{12}O_2N_2Cl_2$	57.33	3.61	8.36	57.17	4.00	8.24
II-15	6-Cl	2′-CH_3	4′-Cl	MeOH	157—158	54	$C_{16}H_{12}O_2N_2Cl_2$	—	—	8.36	—	—	8.18

a) uncorrected

TABLE III.



III

Compd. No.	R_1	R_2	R_3	R_4	mp[a] (°C)	Recrys. solv.
III-1	H	4'-Cl	H	$(CH_3)_2N-CH_2-CH_2-$	93—95	toluene
III-2	H	4'-Cl	H	$(CH_3)_2N-CH_2-CH_2-CH_2-$	110—112	
III-3	H	4'-OCH	H	$(CH_3)_2N-CH_2-CH_2-$	157—158	benzene
III-4	H	4'-CH_3	H	$(CH_3)_2N-CH_2-CH_2-$	123—124	EtOH-H_2O

Compd. No.	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
III-1	$C_{19}H_{20}O_2N_3Cl$	63.77	5.63	11.74	64.02	5.59	11.93
III-2	$C_{20}H_{22}O_2N_3Cl$	—	—	9.53	—	—	9.77
III-3	$C_{20}H_{22}O_3N_3$	67.96	6.56	11.89	67.81	6.54	11.77
III-4	$C_{20}H_{22}O_2N_3$	71.19	6.87	12.45	71.32	6.90	12.39

a) uncorrected

o-Nitrobenzoyl chloride derivatives are reacted with anilines to give corresponding *o*-nitrobenzanilides, which are reduced with iron powder, water and ammonium chloride to corresponding *o*-aminobenzoylanilides. The chloroacetylation with chloroacetyl chloride affords *o*-chloroacetamidobenzanilides (I). The treatment of compound I with triethyl amine in ethylene glycol monomethyl ether causes the production of 4-phenyl-1H-3,4-dihydro-1,4-benzodiazepine-2,5-diones (II), but the heating of compound I with phosphorus trichloride in toluene gives 2-chloromethyl-3-phenylqunazoline-4-one (IV).

Moreover, compound II is treated with sodium amide in toluene, followed by with dialkylaminoalkylchloride to yield a 1-dialkylaminoalkyl-substituted 1,4-benzodiazepine derivative (III).

These compounds were prepared for pharmacological tests on a central nervous system. Among these compounds several compounds showed potent tranquillizing activities, on which will be published in a good opportunity.

Experimental

General Method

2-Chloroacetamidobenzanilides (I)——To a stirred solution of 0.1 mole of anilines and 9 g of pyridine in 60 ml of dry ether was added dropwise 0.1 mole of *o*-nitrobenzoyl chlorides in dry ether. After stirring at room temperature for 2 hr, the solvent was removed *in vacuo* to a solidal residue, which was washed with water to give 2-nitrobenzanilides quantitatively.

A mixture of 0.1 mole of 2-nitrobenzanilides, 34.6 g of ammonium chloride, 34.6 g of iron powder, 140 ml of water and 300 ml of methanol was heated under reflux for 2—3 hr with stirring. The precipitate was removed by hot filtration and washed with 300 ml of hot methanol. The filtrate was poured into 600 ml of water. After cooling, the precipitate was collected by filtration, washed with water and dried to give 2-aminobenzanilides.

While a mixture of 0.11 mole of chloroacetyl chloride and an equimolar amount of 3N sodium hydroxide aqueous solution was added dropwise to a suspension of 0.1 mole of 2-aminobenzanilides in methyl chloroacetate, the mixture was kept below 10° and neutral or slightly alkaline. After the addition, the stirring was continued at room temperature for additional 2 hr. The precipitate was collected by filtration, and washed with water to give crystals of compound I.

4-Aryl-1H-3,4-dihydro-1,4-benzodiazepine-2,5-diones (II)——A mixture of 0.1 mole of 2-chloroacetamidobenzanilide derivative, 0.11 mole of triethylamine and 0.04 mole of potassium carbonate and 240 ml of ethylene glycol monomethyl ether was heated at 50—80 for 5hr—2 days. After cooling, the reaction mixture was filtered and concentrated *in vacuo*. The crystalline precipitate was collected by filtration and washed with water and them a small amount of methanol to give crystals of compound II.

1-[2-(Dimethylamino)ethyl]-4-aryl-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione (III)——A typical procedure for preparation of compound II is shown by the following preparation of 1-[2-(dimethylamino)-ethyl]-4-(*p*-methoxyphenyl)-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione (III-3).

To a suspension of sodium amide prepared from 2 g of sodium and liq. NH_3 in 400 ml of dry toluene was added a mixture of 15.0 g (0.0539 mole) of 4-(*p*-methoxyphenyl)-3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione (II-5) and 150 ml of toluene. The mixture was heated at 60—70 ° for 2 hr with stirring until the occurence of ammonia gas ceased. Thereto was added a solution of 9.5 g of 2-dimethylaminoethyl chloride in 95 ml of dry toluene and the mixture was heated at 95—105° for 4 hr with stirring. After cooling, the resultant mixture was washed with 100 ml of water twice and extracted with 1N hydrochloric acid. The aqueous layer was made alkaline with 28.5% NaOH, and the precipitate was collected by filtration and washed with water to give 11 g of crude compound III-3, mp 151—153°. Recrystallization from benzene gave compound III-3, mp 157—158°.

2-Chloromethyl-3-(2-methyl-4-chlorophenyl)-5-chloro-3H-quinazoline-4-one (IV)——A solution of 0.5 g of phosphorus trichloride in 5 ml of toluene was added dropwise to a suspension of 2.6 g of 2-chloroacetamido-4′,6-dichloro-2′-methylbenzanilide in 50 ml of toluene. The mixture was heated under reflux for 5 hr. After cooling, 24 ml of 10% sodium carbonate was added to the reaction mixture with stirring, and the stirring was continued for an additional 1 hr. The precipitate was removed by the filtration. The organic layer of the filtrate was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure to dryness. The residual solid was recrystallized from benzene–petroleum ether to give 0.8 g of 2-chloromethyl-3-(2-methyl-4-chlorophenyl)-5-chloro-3H-qunazoline-4-one, mp 162—170°. Recrystallization from benzene gave an analytical material, mp 183—185°. IR $\nu_{max}^{paraffin}$ (cm^{-1}): 1693, 1610, 1593, 1550. *Anal.* Calcd. for $C_{16}H_{11}ON_2Cl_3$: C, 54.33; H, 3.11; N, 7.92. Found: C, 54.42; H, 2.94; N, 7.64.