amine (excitation in rats[26]) and yohimbine (toxicity in mice[27]). Sympatholytic action was measured by the blockade of the carotid occlusion reflex in the dog under pentobarbital, and parasympatholytic activity by the mydriasis produced in mice (Pulewka method[28]). In order to prevent interference by mydriasis produced via a potentiation of sympathetic mechanisms the mice were pretreated with reserpine. "Tranquillizing" action was assessed by measuring the induction and duration of sleep in mice after a non-narcotic dose of ethanol (5 ml./kg. p.o.); the dose of drug to produce a mean duration of sleep of 50 min. was determined.

Results

In the various tests for antagonism to reserpine and potentiation of adrenergic agents, the dimethylaminopropyl derivative of each ring system showed optimum activity and was taken as the representative member. A comparison of the effective doses of the dimethylaminopropyl derivatives of four ring systems with those of imipramine (I) is given in Table III.

For antagonism to reserpine actions, only the dibenzodiazepine derivative XVIIIa showed activity comparable to imipramine; except for the derivative of 5-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XI) in the test for reversal of reserpine-induced ptosis, the other derivatives showed weak or no activity. A somewhat similar picture was shown in the tests of potentiation of adrenergic agents, although all derivatives potentiated the pressor response to norepinephrine in doses of 0.1–0.4 mg./kg. The dibenzodiazepine derivative (XVIIIa) was markedly more potent than imipramine in the tests to detect sympatholytic, "tranquillizing" and parasympatholytic activity. In the former two tests, its potency approached that of the corresponding phenothiazine derivative, promazine (II). The other three compounds displayed negligible activity in all three tests.

The dibenzodiazepine derivative (XVIIIa) thus showed activity in all tests comparable to or greater than that of imipramine. In dogs, cats and monkeys, however, it was found to induce convulsions when given in doses about double those necessary to antagonize certain effects of reserpine. In dogs and cats repeated doses gave rise to leucocytopoenia and liver damage.

The monomethylaminopropyl derivatives of the dibenzazocine (V), 5-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XI) and 10,11-dihydrodibenz[b,f]azepine (desmethyl imipramine) systems showed greater potency than their dimethylated homologs in the tests for antagonism to reserpine and potentiation of adrenergic agents, but less sympatholytic, "tranquillizing" and parasympatholytic properties.

Acknowledgment.—The authors wish to thank Mr. P. Wood and his staff of this department for microanalyses.

(26) G. Halliwell and R. M. Quinton, to be published.
(27) R. M. Quinton, *Brit. J. Pharmacol.*, in press.
(28) P. Pulewka, *Arch. Exp. Pathol. Pharmakol.*, **168**, 307 (1932).

Quinazolines and 1,4-Benzodiazepines. X.[1] Nitro-Substituted 5-Phenyl-1,4-benzodiazepine Derivatives[2]

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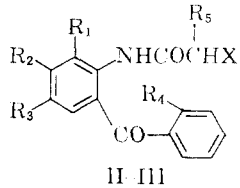
The general synthesis of nitro-substituted 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones from aminonitrobenzophenones and the specific synthesis of 1,3-dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones by direct nitration of the corresponding unsubstituted benzodiazepinones is described. The position of the nitro group was proved by its replacement by chlorine *via* a Sandmeyer reaction of the amine obtained by reduction. Alkylation of some of the benzodiazepinones gave the corresponding 1-alkyl derivatives. Mild acid hydrolysis of nitrobenzodiazepinones and 1-alkyl-nitrobenzodiazepinones led to several previously undescribed aminonitrobenzophenones. 2-Amino-5-nitrobenzophenone was converted *via* the α-oxime into the corresponding 2-chloromethyl-6-nitro-4-phenylquinazoline 3-oxide and this compound when treated with nucleophilic reagents gave, by a ring expansion, 1,3-dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide. The pharmacological properties of three nitrobenzodiazepine derivatives are reported. These compounds showed a low toxicity combined with sedative, muscle relaxant and anticonvulsant properties.

Our interest in the new class of psychotherapeutic agents, 1,4-benzodiazepines, led us to prepare a series of 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones (IV) bearing nitro groups on the nucleus and the 5-phenyl substituent. Two general methods for the preparation of nitrobenzodiazepinones were employed. The first (Chart 1) consisted of treating the bromoacetamido derivatives II(a,b,c,e) (Table I) of the known aminonitrobenzophenones I(a,b,c,e)[3] with ammonia and cyclizing the products III to the benzodiazepinones IV using essentially the procedures described previously.[4] Reaction of Ic with 2-bromopropionyl bromide, instead of bromoacetyl bromide, followed by ammonolysis, gave the aminopropionamido derivative IIId which, on ring closure, yielded 1,3-dihydro-3-methyl-7-nitro 5-phenyl-2*H*-1,4-benzodiazepin-2-one (IVd).

(1) Paper IX, A. Stempel and F. W. Landgraf, *J. Org. Chem.*, **27**, 4675 (1962).
(2) Presented in part at the Gordon Research Conference on Medicinal Chemistry, August, 1961. The pharmacological data were presented by Dr. G. Heise.
(3) 2-Amino-3-nitrobenzophenone (Ia), 2-amino-4-nitrobenzophenone (Ib), 2-amino-5-nitrobenzophenone (Ic): K. Schofield and R. S. Theobald, *J. Chem. Soc.*, 1505 (1950). 2-Amino-2′-nitrobenzophenone (Ie): D. H. Hey and R. D. Mulley, *J. Chem. Soc.*, 2276 (1952).
(4) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).

TABLE I

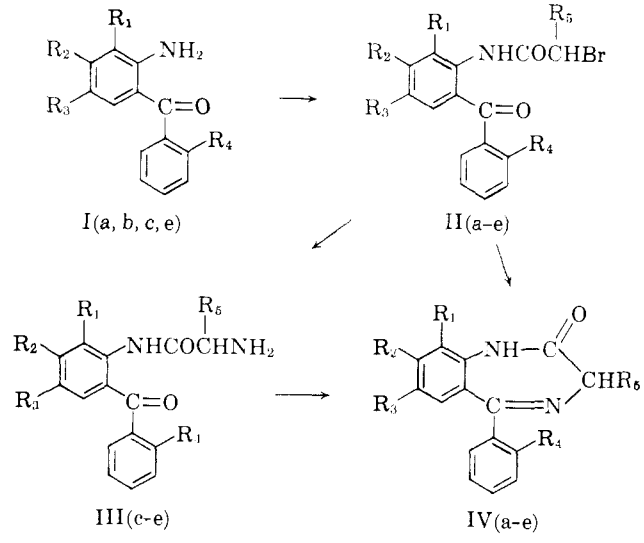
2-ACYLAMINOBENZOPHENONES



II–III

Compound	R_1	R_2	R_3	R_4	R_5	X	Method[a]	Cryst.[b] from	Formula	M.p., °C.	%C Carbon Calcd.	%C Carbon Found	%H Hydrogen Calcd.	%H Hydrogen Found
IIa[c]	NO_2	H	H	H	H	Br	D	Et_2O	$C_{15}H_{11}BrN_2O_4$	120.5–121.5	49.61	49.70	3.05	3.29
IIb[c]	H	NO_2	H	H	H	Br	A	Hex/$CHCl_3$	$C_{15}H_{11}BrN_2O_4$	120–121	49.61	49.39	3.05	2.85
IIc	H	H	NO_2	H	H	Br	D	Et_2O	$C_{15}H_{11}BrN_2O_4$	155–156	49.61	49.65	3.05	3.43
IId	H	H	NO_2	H	CH_3	Br	D	Et_2O	$C_{16}H_{13}BrN_2O_4$	111–114	50.95	50.82	3.47	3.53
IIe	H	H	H	NO_2	H	Br	D	C_6H_6	$C_{15}H_{11}BrN_2O_4$	157–159	49.61	49.58	3.05	3.32
IIj	H	H	H	Cl	H	Br	D	MeOH	$C_{16}H_{11}BrClNO_2$	119–121	51.09	51.32	3.14	3.36
IIIc	H	H	NO_2	H	H	NH_2	K	$Et_2O/CHCl_3$	$C_{15}H_{13}N_3O_4$	166–167	60.19	60.33	4.38	4.54
IIId	H	H	NO_2	H	CH_3	NH_2	H	EtOH	$C_{16}H_{15}N_3O_4$	155–156	61.33	61.58	4.83	4.78
IIIe	H	H	H	NO_2	H	NH_2	H	EtOH	$C_{15}H_{13}N_3O_4$	157–159	60.19	60.32	4.38	4.46
IIIj	H	H	H	Cl	H	NH_2	H	EtOH	$C_{15}H_{13}ClN_2O_2$	162–164	62.40	62.56	4.54	4.57

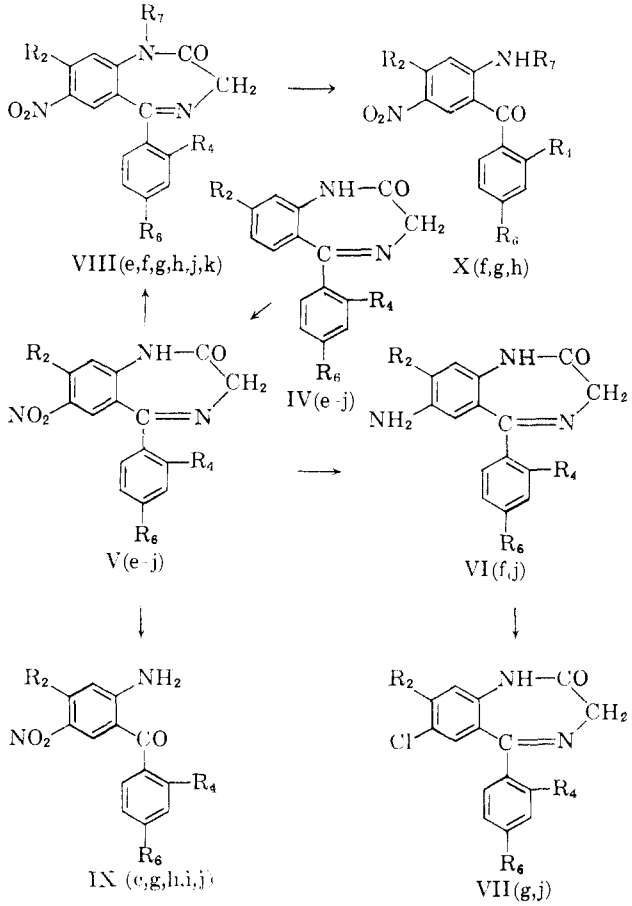
[a] The letters denoting the method of preparation refer to the Experimental section of paper VI in this series.[4] [b] Et_2O = ethyl ether, Hex = hexane, EtOH = ethanol, C_6H_6 = benzene, MeOH = methanol. [c] As previously reported,[4] in some instances only benzodiazepinones were isolated from the ammonolysis reaction.



I(a, b, c, e) II(a–e) III(c–e) IV(a–e)

(a) $R_1 = NO_2$; $R_2 = R_3 = R_4 = H$
(b) $R_2 = NO_2$; $R_1 = R_3 = R_4 = R_5 = H$
(c) $R_3 = NO_2$; $R_1 = R_2 = R_4 = R_5 = H$
(d) $R_3 = NO_2$; $R_5 = CH_3$; $R_1 = R_2 = R_4 = H$
(e) $R_4 = NO_2$; $R_1 = R_2 = R_3 = R_5 = H$

Chart 1



VIII(e,f,g,h,j,k) X(f,g,h) IV(e–j) V(e–j) VI(f,j) IX (e,g,h,i,j) VII(g,j)

(e) $R_4 = NO_2$; $R_2 = R_6 = H$ (in VIII, $R_7 = CH_3$)
(f) $R_2 = R_4 = R_6 = H$ (in VIII and X, $R_7 = CH_3$)
(g) $R_4 = F$; $R_2 = R_6 = H$ (in VIII and X, $R_7 = CH_3$)
(h) $R_6 = Cl$; $R_2 = R_4 = H$ (in VIII and X, $R_7 = CH_3$)
(i) $R_2 = CH_3$; $R_4 = R_6 = H$
(j) $R_4 = Cl$; $R_2 = R_6 = H$ (in VIII, $R_7 = CH_3$)
(k) R_7 = 3-methylbutyl; $R_2 = R_4 = R_6 = H$

Chart 2

The second method (Chart 2) of obtaining these compounds was direct nitration of the benzodiazepinones IV(e–k) with a mixture of concentrated sulfuric acid and potassium nitrate. In all cases a slight excess of the nitrating agent was used, and a single mononitro derivative was obtained. Starting material could usually be recovered from the reaction mixture, while in two cases (from compounds IVf and IVg) dinitrobenzodiazepinones were isolated as by-products.[5]

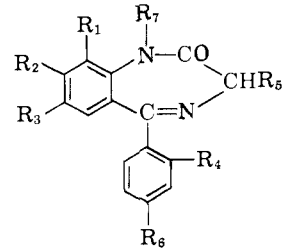
As expected, nitration occurred at position 7 of the benzodiazepinone nucleus. This was shown by a direct comparison of Vf, obtained by nitration of 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (IVf),[6] with IVc, prepared from 2-amino-5-nitrobenzophenone (Ic). Mixture melting point determinations and a comparison

(5) The preparation and proof of structure of these compounds will be reported in a later publication.

(6) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962).

TABLE II

5-PHENYL-1,4-BENZODIAZEPIN-2-ONES



IV, V, VI, VIII

Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Method[a]	Cryst.[b] from	Formula	M.p., °C.	% Carbon Calcd.	% Carbon Found	% Hydrogen[c] Calcd.	% Hydrogen[c] Found
IVa	NO_2	H	H	H	H	H	H	L	EtOH	$C_{15}H_{11}N_3O_3$	144–145	64.05	63.81	3.94	3.66
IVb	H	NO_2	H	H	H	H	H	L	EtOH	$C_{15}H_{11}N_3O_3$	262 dec.	64.05	64.31	3.94	4.28
IVc	H	H	NO_2	H	H	H	H	L, Q	EtOH	$C_{15}H_{11}N_3O_3$	224–226	64.05	64.02	3.94	3.80
IVd	H	H	NO_2	H	CH_3	H	H	L	C_6H_6/hex.	$C_{16}H_{13}N_3O_3$	221–222	65.08	64.85	4.44	4.41
IVe	H	H	H	NO_2	H	H	H	N[1]	C_6H_6	$C_{15}H_{11}N_3O_3$	206–208	64.05	64.10	3.94	4.02
IVh	H	H	H	H	H	Cl	H	Q	EtOH	$C_{15}H_{11}ClN_2O$	262–263	66.55	66.96	4.10	3.91
IVi	H	CH_3	H	H	H	H	H	Q	MeOH	$C_{16}H_{14}N_2O$	255–256	76.78	76.20	5.64	5.68
IVj	H	H	H	Cl	H	H	H	N[1]	MeOH	$C_{15}H_{11}ClN_2O$	212–213	66.55	66.27	4.11	4.27
Ve	H	H	NO_2	NO_2	H	H	H	*d*	THF	$C_{15}H_{10}N_4O_5$	226–228	55.22	55.43	3.09	2.97
Vf	H	H	NO_2	H	H	H	H	*d*	EtOH	$C_{15}H_{11}N_3O_3$	224–226	64.05	64.30	3.94	4.09
Vg	H	H	NO_2	F	H	H	H	*d*	Ac	$C_{15}H_{10}FN_3O_3$	210–211	60.20	60.00	3.37	3.49
Vh	H	H	NO_2	H	H	Cl	H	*d*	CH_2Cl_2	$C_{15}H_{10}ClN_3O_3$	253–254	57.06	56.98	3.19	3.07
Vi	H	CH_3	NO_2	H	H	H	H	*d*	C_6H_6	$C_{16}H_{13}N_3O_3$	218–219	65.08	64.98	4.40	4.62
Vj	H	H	NO_2	Cl	H	H	H	*d*	CH_2Cl_2	$C_{15}H_{10}ClN_3O_3$	238–240	57.06	57.30	3.19	3.07
VIf	H	H	NH_2	H	H	H	H	*d*	EtOH	$C_{15}H_{13}N_3O$	228–231	71.71	71.41	5.18	5.09
VIg	H	H	NH_2	F	H	H	H	*d*	EtOH	$C_{15}H_{12}FN_3O$	264–266	66.90	67.01	4.49	5.54
VIj	H	H	NH_2	Cl	H	H	H	*d*	EtOH	$C_{15}H_{12}ClN_3O$	230–232	63.05	62.94	4.23	4.50
VIIIe	H	H	NO_2	NO_2	H	H	CH_3	*d*	MeOH	$C_{16}H_{12}N_4O_5$	209–212	56.47	56.33	3.55	3.58
VIIIf	H	H	NO_2	H	H	H	CH_3	*d*	EtOH	$C_{16}H_{13}N_3O_3$	156–157	65.09	65.34	4.41	4.64
VIIIg	H	H	NO_2	F	H	H	CH_3	*d*	CH_2Cl_2/hex.	$C_{16}H_{12}FN_3O_3$	170–172	61.34	61.43	3.86	3.68
VIIIh	H	H	NO_2	H	H	Cl	CH_3	*d*	Ac/hex.	$C_{16}H_{12}ClN_3O_3$	131–135	58.28	58.63	3.67	3.56
VIIIj	H	H	NO_2	Cl	H	H	CH_3	*d*	Et_2O	$C_{16}H_{12}ClN_3O_3$	194–195	58.28	58.20	3.67	3.58
VIIIk	H	H	NO_2	H	H	H	$CH_2CH_2CH(CH_3)_2$	*d*	Et_2O	$C_{20}H_{21}N_3O_3$	121–122	68.36	68.59	6.02	6.17

[a] The letters denoting the method of preparation for compounds IV refer to the Experimental section of paper VI in this series.[4] [b] EtOH = ethanol, C_6H_6 = benzene, hex. = hexane, MeOH = methanol, THF = tetrahydrofuran, Ac = acetone, Et_2O = diethyl ether. [c] In some cases also the nitrogen and halogens have been determined. [d] See Experimental part for compounds of type V, VI, and VIII.

of infrared spectra showed these two compounds to be identical. Additional proof was obtained, as discussed below, for compounds IVg and j, which on nitration gave the 7-nitro derivatives Vg and j.

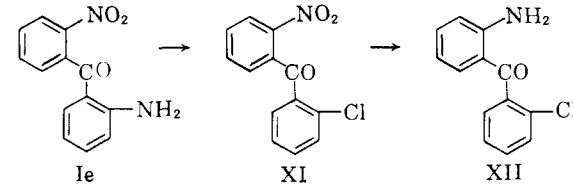
Hydrogenation of the nitrobenzodiazepinones V-(f,g,j) in the presence of Raney nickel afforded the amino compounds VI (Table II). The aminobenzodiazepinones VI(g,j) were converted, *via* Sandmeyer reactions, into the corresponding chlorobenzodiazepinones VII. These compounds were shown to be identical with the corresponding, known 7-chlorobenzodiazepinones[4] by the usual criteria. By analogy, structures Ve,h, and i were assigned to the nitration products of IVe,h, and i, respectively. It was also observed that hydrolysis of Vi gave a 2-amino-4-methylnitrobenzophenone (IXi) which had the same melting point (177–178°) as the 2-amino-4-methyl-5-nitrobenzophenone described in the literature.[7]

Treatment of the nitrobenzodiazepinones Ve,f,g,h and j with sodium methoxide and the appropriate alkylating agent[4] afforded the 1-alkyl-substituted compounds (Table II) VIIIe,f,g,h,j (R_7 = CH_3) and VIIIk [R_7 = $CH_2CH_2CH(CH_3)_2$], respectively.

Mild acid hydrolysis of the)nitrobenzodiazepinones (V) and the alkyl nitrobenzodiazepinones (VIII) gave several new 2-aminonitrobenzophenones (IX) and 2-alkyl-aminonitrobenzophenones (X). These compounds are listed in Table III.

Except for IVh, IVi, and IVj, all the benzodiazepinones used as starting materials for the nitration have been reported previously.[4,6] Compounds IVh and IVi (Table II) were synthesized from known aminobenzophenones[8] by condensation with glycine ethyl ester hydrochloride, a method described in an earlier paper.[4]

The benzodiazepinone IVj was obtained *via* the aminoacetamido derivative IIIj (Table I) of the heretofore undescribed 2-amino-2′-chlorobenzophenone (XII). This aminobenzophenone (XII), in turn, was prepared as shown below from Ie *via* a Sandmeyer reaction followed by catalytic hydrogenation of the resulting 2-chloro-2′-nitrobenzophenone (XI).



Ie XI XII

The preparation of 7-nitro-5-phenyl-1,4-benzodiazepine 4-oxides was carried out as follows: 2-amino-5-nitrobenzophenone (Ic) was converted into the α-oxime (XIII)[9] which was transformed by known methods[10]

(7) L. Chardonnens and C. Perriard, *Helv. Chim. Acta*, **28**, 593 (1945)

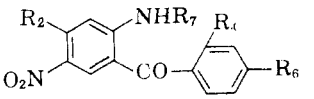
(8) 2-Amino-4′-chlorobenzophenone: K. Suzuki, E. Weisburger, and J. Weisburger, *J. Org. Chem.*, **26**, 2239 (1961). 2-Amino-4-methylbenzophenone: E. Ritchie, *J. Proc. Roy. Soc. N. S. Wales*, **80**, 33 (1946).

(9) The α-configuration was ascribed to this oxime on the basis of its infrared spectrum which shows a broad band at 3400 to 3200 cm.$^{-1}$, characteristic of bonded hydrogen for the α-form.[10]

(10) L. H. Sternbach S. Kaiser and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).

TABLE III

2-AMINO-5-NITROBENZOPHENONES



IX—X

Compound	R_2	R_4	R_6	R_7	Cryst.[a] from	Formula	M.p. °C.	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found
IXe	H	NO_2	H	H	C_6H_6	$C_{13}H_9N_3O_5$	199–202	54.36	54.24	3.16	3.47
IXg	H	F	H	H	Et_2O	$C_{13}H_9FN_2O_3$	154–158	60.00	59.82	3.47	3.59
IXh	H	H	Cl	H	EtOH	$C_{13}H_9ClN_2O_3$	196–197	56.43	56.62	3.28	3.47
IXj	H	Cl	H	H	EtOH	$C_{13}H_9ClN_2O_3$	118–120	56.43	56.12	3.28	3.31
Xf	H	H	H	CH_3	EtOH	$C_{14}H_{12}N_2O_3$	159–161	65.50	66.05	4.68	4.38
Xg	H	F	H	CH_3	MeOH	$C_{14}H_{11}FN_2O_3$	186–187	61.31	61.46	4.04	4.08
Xh	H	H	Cl	CH_3	MeOH	$C_{14}H_{11}ClN_2O_3$	207–208	57.84	57.99	3.81	3.85

[a] C_6H_6 = benzene, Et_2O = diethyl ether, EtOH = ethanol, MeOH = methanol.

TABLE IV

PHARMACOLOGICAL DATA[a]

Compound	Mice-LD_{50} mg./kg. P.O. Mice LD_{50} mg./kg. i.p.	Mice-ED_{50} mg./kg. P.O. Inclined screen	Foot-shock	Anti-strychnine	Cat[b] MED mg./kg. P.O.	Antipenta-methylene-tetrazole	Max. Electro-shock	Min. Electro-shock
Chlordiazepoxide	268	100	40	87	2	18	95	100
Vf[c]	275	15[d]	5	20	0.1	0.5	8	132
XVIa	>400	250	>100	[e]	[e]	35	112	>800
XVIb	>500	200	100	[e]	[e]	5	183	>800

[a] These tests, with the exception of the footshock test, are described by L. O. Randall, W. Schallek, G. A. Heise, E. Keith, and R. Bagdon, *J. Pharmacol. Exp. Therap.*, **129**, 163 (1960). The footshock test has been described by R. E. Tedeschi, D. D. Tedeschi, A. Mucha, L. Cook, P. A. Mattis, and E. J. Fellows, *ibid.*, **125**, 28 (1959). [b] Minimum effective dose at which muscle relaxation and ataxia was obtained. [c] Depressant effects on conditioned avoidance behavior have been described by G. A. Heise and E. Boff, *Psychopharmacologia*, **3**, 264 (1962). [d] Hyperactivity was observed, even at the muscle relaxant dose. [e] Not determined.

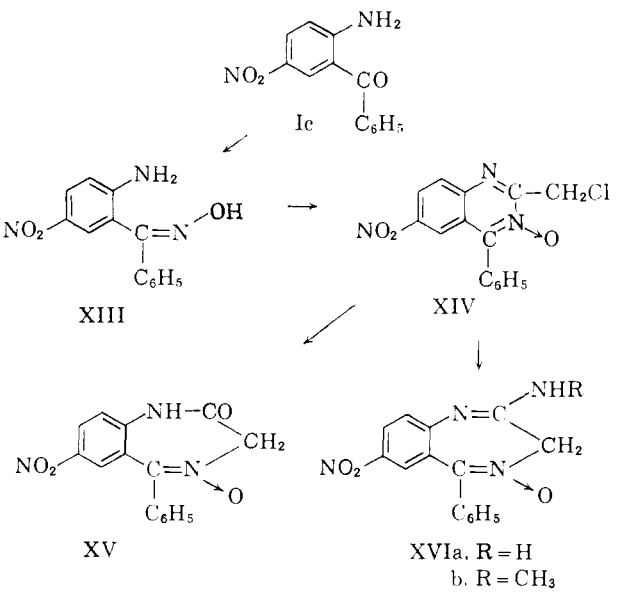


Chart 3

to the chloromethylquinazoline 3-oxide (XIV) (Chart 3). It was found that this compound, in analogy with previously reported cases,[11] underwent ring enlargement on treatment with nucleophilic reagents to form the corresponding 1,4-benzodiazepine 4-oxides in excellent yield.

The reaction of XIV with alkali gave the benzodiazepinone 4-oxide (XV).

When XIV was treated with either ammonia or methylamine, amino- and methylaminobenzodiazepine 4-oxides (XVIa and XVIb) were obtained, respectively. The structures of all these compounds were confirmed by a comparison of their infrared spectra with those of known[11a,c] analogs.

A pharmacological study of three 7-nitrobenzodiazepine derivatives, Vf, XVIa, and XVIb, showed that they possessed interesting muscle relaxant, sedative and anticonvulsant activities (Table IV). It can be seen that, as a sedative and muscle relaxant, compound Vf[12] is approximately 7 times as active in the mouse (inclined screen test) and about 20 times as active in the cat as was chlordiazepoxide (7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide). The other two compounds were less active than chlordiazepoxide. The pharmacological studies of the other compounds discussed in this paper have not yet been completed.

Experimental

All melting points are corrected. The infrared spectra were determined in 1–5% chloroform solution using a Perkin–Elmer Model 21 spectrophotometer.

1,3-Dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones (V, e-j) (Table III).—A solution of 0.12 mole of potassium nitrate[13] in 25 ml. of concd. sulfuric acid was added dropwise to a solution of 0.1 mole of the 1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one IV in 50 ml. of concd. sulfuric acid. The mixture was heated on a water bath to 45–50°, stirred for approximately 3 hr.,[14]

(11) (a) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961); (b) L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *ibid.*, **26**, 4488 (1961); (c) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 4936 (1961).

(12) A preliminary report of the pharmacological properties of this compound appeared earlier. L. O. Randall and B. Kappell, *Biochem. Pharmacol.*, **8**, 15 (1961).

(13) Fuming nitric acid has also been used as the nitrating agent in the reaction but was found to give unreproducible results and greater quantities of the dinitrated product.[5]

(14) For the preparation of compounds Vf and Vg, better yields were obtained if the reaction was run at −5–0° and stirred for approximately 8 hr.

cooled and poured over ice. After neutralizing with ammonia, the precipitate was filtered, washed with water and dissolved in dichloromethane.[15] The solution was dried over anhydrous sodium sulfate, filtered and concentrated to an oil, which was dissolved in the appropriate solvent and allowed to crystallize.

7-Amino-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones (VI, f,g,j) (**Table** II).—A solution of 0.032 mole of 1,3-dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one (IV) in 1 l. of ethanol was hydrogenated at 25° and 1 atm. in the presence of 0.6 g. of wet (ethanol) Raney nickel catalyst (No. 28). The hydrogenation stopped after the uptake of 0.096 mole of hydrogen. The solution was filtered from the catalyst and concentrated *in vacuo* to give yellow needles, which were filtered and recrystallized from ethanol.

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones (VII, g, j).—A solution of 8.6 mmoles of VI in 10 ml. of 6 *N* hydrochloric acid was diazotized with an aqueous solution of 9.5 mmoles of sodium nitrite at 0–5°. The resulting solution was added to 4 g. of cuprous chloride dissolved in 40 ml. of 3 *N* hydrochloric acid. The mixture was heated on a steam bath for 30 min. to complete the liberation of nitrogen. After cooling, the green solid which had separated was collected on a filter and dissolved in dichloromethane. Copper salts were removed by washing the dichloromethane solution with aqueous ammonia and the almost colorless solution was then dried over sodium sulfate and evaporated to give a colorless oil which was crystallized from ethanol. The products (VII g,j) were compared with (infrared spectra and mixture m.p.) and shown to be identical with the corresponding authentic 7-chlorobenzodiazepinones.[4]

1-Alkyl-1,3-dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-ones (VIII, e, f, g, h, j, k) (**Table** II).—A mixture of 0.05 mole of V, 50 ml. of N,N-dimethylformamide and 0.06 mole of sodium methoxide was stirred at room temperature for 30 min. The solution of the sodio derivative was cooled to 5° and 0.73 mole of methyl iodide[16] was slowly added. The reaction mixture was stirred at 5° for 1 hr., poured into 1 l. of water, and the product was extracted into methylene chloride (3 × 100 ml.). The organic layers were combined, washed with water (3 × 100 ml.), dried over sodium sulfate, filtered and concentrated to an oil. The residue was cyrstallized from the appropriate solvent.

2-Aminonitrobenzophenones (IXe, g, h, i, j) and 2-Alkylaminonitrobenzophenones (X, f, g, h) (**Table** III).—A solution of 10 g. of benzodiazepinone V or VIII in a mixture of 250 ml. of ethanol and 250 ml. of 3 *N* hydrochloric acid was heated under reflux for 3 hr. Ethanol was removed under reduced pressure and the solution cooled. The product was filtered and recrystallized from the appropriate solvent.

2-Chloro-2′-nitrobenzophenone (XI).—A solution of 21.5 g. of sodium nitrite in 50 ml. of water was slowly added (3 hr.) to a stirred solution of 75 g. (0.33 mole) of 2-amino-2′-nitrobenzophenone (Ie)[3] in 700 ml. of concentrated hydrochloric acid at 0°. The temperature of the suspension was kept at 2–7° during the addition. The resulting clear solution was poured into a stirred solution of 37 g. of cuprous chloride in 350 ml. of 6 *N* hydrochloric acid. The solid, which formed after a few min., was collected on a filter, washed with water and recrystallized from ethanol to give 66 g. (81%) of product, m.p. 76–79°.

Anal. Calcd. for $C_{13}H_8ClNO_3$: C, 59.67; H, 3.08. Found: C, 59.75; H, 3.15.

2-Amino-2′-chlorobenzophenone (XII).—A solution of 20 g. (0.081 mole) of 2-chloro-2′-nitrobenzophenone (XI) in 450 ml. of ethanol was hydrogenated at 25° and 1 atm. with Raney nickel catalyst (No. 28). After an uptake of 6 l. of hydrogen, the solution was filtered from the catalyst and the alcohol was removed under reduced pressure. The residue was distilled in a bulb tube at 0.4 mm. and a bath temperature of 150–165° to give 15.8 g. (90%) of a yellow oil. A small sample was dissolved in alcohol which, on the addition of water, crystallized to give needles, m.p. 58–60°.

Anal. Calcd. for $C_{13}H_{10}ClNO$: C, 67.39; H, 4.35. Found: C, 66.99; H, 4.34.

2-Amino-5-nitrobenzophenone Oxime (XIII).—A mixture of 72 g. (0.3 mole) of 2-amino-5-nitrobenzophenone, 500 ml. of ethanol, 25 ml. of water, 34 g. (0.49 mole) of hydroxylamine hydrochloride, and 90 g. of potassium hydroxide was heated on the steam bath with stirring for 15 min. The reaction mixture was cooled to room temperature and poured into 1 l. of 1.5 *N* hydrochloric acid. The crude product was filtered and dried to give a yield of 71 g. (92%) of product, m.p. 195–200°. The pure compound crystallized from ethanol as pale yellow needles, m.p. 203–205°.

Anal. Calcd. for $C_{13}H_{11}N_3O_3$: C, 60.78; H, 4.28. Found: C, 60.62; H, 4.69.

2-Chloromethyl-4-phenyl-6-nitroquinazoline 3-Oxide (XIV).—To a warmed (50–60°), stirred suspension of 10 g. (0.039 mole) of 2-amino-5-nitrobenzophenone oxime in 100 ml. of acetic acid, 6 ml. (0.08 mole) of chloroacetyl chloride was added in small portions. The mixture was allowed to stand overnight at room temperature and then concentrated *in vacuo*. The residue was crystallized from a mixture of acetone and methylene chloride to give 5.8 g. of the pure compound as yellow prisms, m.p. 205–207°.

Anal. Calcd. for $C_{15}H_{10}ClN_3O_3$: C, 56.96; H, 3.16. Found: C, 56.62; H, 3.36.

1,3-Dihydro-7-nitro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-Oxide (XV).—To a suspension of 6.3 g. (0.02 mole) of XIV in a mixture of 50 ml. of ethanol and 20 ml. of acetone, 24 ml. of *N* sodium hydroxide solution was added dropwise. The reaction mixture was warmed to 40° and then stirred at room temperature overnight. The mixture was then adjusted to pH 5 with dilute hydrochloric acid and concentrated to dryness *in vacuo*. The residue was digested with a mixture of 125 ml. of ethanol and 30 ml. of acetone and the product obtained from the filtrate by precipitation with petroleum ether. The product was recrystallized from an ethanol–petroleum ether mixture to give 1.95 g. (33%) of compound as yellow prisms, m.p. 218–220° dec.

Anal. Calcd. for $C_{15}H_{11}N_3O_4$: C, 60.61; H, 3.70. Found: C, 61.04; H, 3.92.

2-Amino-7-nitro-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (XVIa).—A suspension of 6.3 g. (0.02 mole) of XIV in 170 ml. of 12% (w/w) ethanolic ammonia was stirred for 24 hr. at room temperature. The yellow crystalline product was filtered and recrystallized from ethanol to give 5.8 g. (97%) of yellow prisms, m.p. 243° dec.

Anal. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.80; H, 4.08. Found: C, 60.42; H, 4.21.

2-Methylamino-7-nitro-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide (XVIb).—To 150 ml. of a cold (5°), stirred solution of methylamine in methanol (25% w/w), 6.3 g. (0.02 mole) of XIV was added in portions. The reaction mixture was stirred at room temperature for 24 hr. and then allowed to stand for another 24 hr. The product was filtered, washed with a little methanol and dried, giving 3.5 g. (59%) of yellow needles, m.p. 256–257° dec. The pure compound crystallized in yellow needles from an ethanol–ether mixture, m.p. 260–261° dec.

Anal. Calcd. for $C_{16}H_{14}N_4O_3$: C, 61.94; H, 4.52. Found: C, 62.03; H, 4.12.

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(15) The insoluble dinitrobenzodiazepinones, which may have formed during the reaction, were removed by filtration at this point.

(16) For compound VIIIk isoamyl bromide was substituted for methyl iodide and the reaction mixture was stirred at 60° for 1 hr.