amine (excitation in rats\textsuperscript{26}) and yohimbine (toxicity in mice\textsuperscript{7}). 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\textsuperscript{27}). 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 30 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 XVIII\textsubscript{a} showed activity comparable to imipramine; except for the derivative of 5-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XI) and 10,11-dihydrodibenzo[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.

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**Quinazolines and 1,4-Benzodiazepines. X.\textsuperscript{1} Nitro-Substituted 5-Phenyl-1,4-benzodiazepine Derivatives\textsuperscript{2}**

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Research Laboratories, Hoffmann-La Roche Inc., Nutley, N. J.

Received September 5, 1962

The general synthesis of nitro-substituted 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-ones from aminonitrobenzophenones and the specific synthesis of 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-ones by direct nitratation 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-chloro-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-2H-1,4-benzodiazepin-2-one 4-oxide. The pharmacological properties of these 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-2H-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 I) consisted of treating the bromoaetamido derivatives II(a,b,c,e) (Table I) of the known aminonitrobenzophenones I(a,b,c,e)\textsuperscript{3} with ammonia and cyclizing the products III to the benzodiazepinones IV using essentially the procedures described previously.\textsuperscript{4} Reaction of Ie with 2-bromopropionyl bromide, instead of bromoaetyl bromide, followed by amnonolysis, gave the aminopropionamido derivative III\textsubscript{d} which, on ring closure, yielded 1,3-dihydro-3-methyl-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one (IVd).

(26) G. Halliwell and R. M. Quinton, to be published.


(2) Presented in part at the Gordon Research Conference on Medicinal Chemistry, August, 1961. The pharmacological data were presented by Dr. G. Heise.


Table 1
2-Acylaminobenzophenones

<table>
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<tr>
<th>Compound</th>
<th>R_1</th>
<th>R_2</th>
<th>R_3</th>
<th>R_4</th>
<th>R_5</th>
<th>Method</th>
<th>Cryst.</th>
<th>Formula</th>
<th>M.p., °C</th>
<th>% Carbon</th>
<th>% Hydrogen</th>
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<tr>
<td>IIa</td>
<td>NO_2</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>D</td>
<td>Et_2O</td>
<td>120.5-121.5</td>
<td>49.61</td>
<td>49.70</td>
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<tr>
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<td>NO_2</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>A</td>
<td>Hex/CHCl</td>
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<td>49.61</td>
<td>49.39</td>
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<tr>
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<td>H</td>
<td>H</td>
<td>NO_2</td>
<td>H</td>
<td>Br</td>
<td>D</td>
<td>Et_2O</td>
<td>155-156</td>
<td>49.61</td>
<td>49.35</td>
</tr>
<tr>
<td>IIe</td>
<td>NO_2</td>
<td>H</td>
<td>H</td>
<td>NO_2</td>
<td>H</td>
<td>Br</td>
<td>D</td>
<td>C_6H_6</td>
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<td>49.38</td>
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<td>H</td>
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<td>H</td>
<td>Br</td>
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<td>Et_2O/CHCl</td>
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<td>H</td>
<td>NH_2</td>
<td>H</td>
<td>H</td>
<td>E_2O</td>
<td>C_6H_12N_2O_4</td>
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<td>NH_2</td>
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<td>C_6H_12N_2O_4</td>
<td>157-159</td>
<td>60.19</td>
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</table>

* The letters denoting the method of preparation refer to the Experimental section of paper VI in this series. 

As expected, nitration occurred at position 7 of the benzodiazepine nucleus. This was shown by a direct comparison of IIj, obtained by nitration of 2-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (IVf), with IVc.

The second method (Chart 2) of obtaining these compounds was direct nitration of the benzodiazepinones IVc-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.

As expected, nitration occurred at position 7 of the benzodiazepinone nucleus. This was shown by a direct comparison of VI, obtained by nitration of 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (IVf), with IVc.

(a) R_1 = NO_2; R_2 = R_5 = R_6 = H
(b) R_1 = NO_2; R_2 = R_4 = R_5 = R_6 = H
(c) R_1 = NO_2; R_2 = R_3 = R_5 = R_6 = H
(d) R_1 = NO_2; R_2 = CH_5; R_3 = R_4 = R_6 = H
(e) R_1 = NO_2; R_2 = R_3 = R_5 = R_6 = H
(f) R_1 = NO_2; R_2 = R_3 = R_6 = H
(g) R_1 = NO_2; R_2 = R_3 = R_6 = H
(h) R_1 = NO_2; R_2 = R_4 = R_6 = H
(i) R_1 = NO_2; R_2 = R_3 = R_6 = H
(j) R_1 = NO_2; R_2 = R_3 = R_6 = H
(k) R_1 = NO_2; R_2 = R_3 = R_6 = H

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,i) in the presence of Raney nickel afforded the amino compounds VIII. These compounds were shown to be identical with the corresponding, known 7-chlorobenzodiazepinones* by the usual criteria. By analogy, structures Ve,h, and i were assigned to the nitration products of IVe,h, and j, respectively. It was also observed that hydrolysis of Vi gave a 2-amino-4-methyl-nitrobenzophenone (IXi) which had the same melting point (177-178°C) 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* afforded the 1-alkyl-substituted compounds (Table II) VIIe,f,g,h,i (R3 = CH2) and VIIh [R7 = CH2CH2CH2CH2], respectively.

Mild acid hydrolysis of the (2-nitrobenzodiazepinones) (V) and the alkyl nitrobenzodiazepinones (VIII) gave several new 2-aminonitrobenzenophenones (IX) and 2-alkylaminonitrobenzenophenones (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.†,‡ Compounds IVh and IVi (Table II) were synthesized from known amino-benzophenones* by condensation with glycine ethyl ester hydrochloride, a method described in an earlier paper.4

The benzodiazepine 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 le via a Sandmeyer reaction followed by catalytic hydrogenation of the resulting 2-chloro-2'-nitrobenzophenone (XI).

The preparation of 7-nitro-5-phenyl-1,4-benzodiazepine 4-oxides was carried out as follows: 2-amino-5-nitrobenzophenone (Ie) was converted into the a-oxime (XIII) which was transformed by known methods8,9

![Diagram of reaction](image)

**Table II**

<table>
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<th>Compound</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
<th>Cryst.</th>
<th>Method*</th>
<th>From</th>
<th>M.p.</th>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>L</td>
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<td>F</td>
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<td>121-122</td>
<td>58.28</td>
<td>3.56</td>
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</table>

* The letters denoting the method of preparation for compounds IV refer to the Experimental section of paper V in this series.4
† EtOH = ethanol, C6H5 = benzene, hex. = hexane, MeOH = methanol, THF = tetrahydrofuran, Ar = acetone, EtO = diethyl ether.
* In some cases also the nitrogen and halogens have been determined.
* See Experimental part for compounds of type V, VI, and VIII.

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10 The a-configuration was assigned 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 a-form.10
It was found that this compound, in analogy with previously reported cases, underwent ring enlargement on treatment with nucleophilic reagents to form the corresponding 1,4-benzodiazepine 3-oxides in excellent yield.

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

When XIV was treated with either ammonia or methanamine, amino- and methylenobenzodiazepine 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 analogs.

A pharmacological study of three 7-nitrobenzodiazepine derivatives, VI, XVla, and XVIIb, 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 VIb is approximately 7 times as active in the mouse (inclined screen test) and about 20 times as active in the cat as was chloridiazepoxide (7-chloro-2-methylaminobenzodiazepine 3-phenyl-3H-1,4-benzodiazepine 4-oxide). The other two compounds were less active than chloridiazepoxide. 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-2H-1,4-benzodiazepin-2-ones V, e-j (Table III). A solution of 0.12 mole of potassium nitrate in 25 ml of concd. sulfuric acid was added dropwise to a solution of 0.1 mole of the 1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one IV in 50 ml of concd. sulfuric acid. The mixture was heated on a water bath to 45–50°C, stirred for approximately 3 hr.,

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(13) Fuming nitric acid has also been used as a nitration agent in the reaction but was found to give unresolvable results and greater quantities of the dinitrated product.

(14) For the preparation of compounds VI and Vg, better yields were obtained if the reaction was run at -5°C 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. 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-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-ones (V, j).

A solution of 8.6 mmol of V in 10 ml of 6 N hydrochloric acid was diazotized with an aqueous solution of 9.3 mmol of sodium nitrite at 0–5°C. 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 dissolving in 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 (V, j) were compared with infrared spectra and mixture m.p. and shown to be identical with the corresponding authentic 7-chlorobenzodiazepinones.

1-Alkyl-1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-ones (VIII, e, f, g, h, j, k).

A solution of 0.05 mmol of V, 50 ml of N,N-dimethylformamide and 0.06 mmol of sodium methoxide was stirred at room temperature for 30 min. The solution of the sodio derivative was cooled to 5° and 0.73 mmol of methyl iodide 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 crystallized from ethanol to give 5.8 g (92%) of yellow needles, m.p. 243° dec.

2-Aminonitrobenzophenones (IX, g, h, i, l) and 2-Alkylamino-nitrobenzophenones (X, f, g, h) (Table III).

A solution of 10 g of benzodiazepine 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 mol) of 2-amino-2'-nitrobenzophenone (180°C) in 700 ml of concentrated hydrochloric acid at 0°C. The temperature of the suspension was kept at 2–7°C 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 of compound as yellow prisms, m.p. 218–220°C dec.

7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-ones (VI, f, g, j) (Table II).

A solution of 0.032 mmol of 1,3-dihydro-7-nitro-5-phenyl-2H-1,4-benzodiazepin-2-one (IV) in 11 ml of ethanol was hydrogenated at 25°C 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 mmol of hydrogen. The reaction mixture was filtered from the catalyst and the alcohol was removed under reduced pressure. The residue was distilled in a bulb at 0.4 mm. and a bath temperature of 150–165°C to give 15.8 g (90%) of a yellow oil. A small sample was dissolved in alcohol on the addition of water, crystallized to give needles, m.p. 58–60°C.

2-Amino-5-nitrobenzophenone Oxime (XIII).

A mixture of 72 g (0.3 mol) of 2-amino-5-nitrobenzophenone, 500 ml of ethanol, 235 ml of water, 34 g (0.49 mol) 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 11 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. 185–205°C. The pure compound crystallized from an ethanol–petroleum ether mixture to 205–206°C.

2-Chloromethyl-4-phenyl-6-nitroquinazoline 3-Oxide (XIV).

To a warmed (45–50°C), stirred suspension of 10 g (0.039 mol) of 2-amino-5-nitrobenzophenone oxime in 100 ml of acetic acid, 1 ml (0.05 mol) of chloroacetyl chloride was added in small portions. The mixture was allowed to stand overnight at room temperature and then concentrated in vacuo to a yellow solid. 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. 205–206°C.

2-Chloromethyl-4-phenyl-6-nitroquinazoline 4-Oxide (XV).

A solution of 6.3 g (0.02 mol) of XIV in a mixture of 50 ml of ethanol and 20 ml of acetic acid, 24 ml of 3 N sodium hydroxide solution was added dropwise. The reaction mixture was warmed to 40°C 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 acetic acid and the product obtained from the filtrate by precipitation with petroleum ether. The product was recrystallized from an ethanol–petroleum ether mixture to 205–206°C.

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