

**5-(2-Diethylaminoethyl)dibenzo[a,d]cycloheptadiene-5-carboxamide.**—A mixture of the carbonitrile (no. 1A) (15.0 g., 0.042 mole) and 90% sulfuric acid (30 ml.) was heated on the steam bath with stirring for 3 hr. It was cooled, poured into ice and water, and the mixture made alkaline with sodium hydroxide. The product was collected in chloroform and the organic layer was dried and evaporated. The residue was converted to the oxalate salt which was recrystallized from ethanol-ether, m.p. 161–162° dec. (12.2 g., 69% yield) (see Table II, no. 9).

**5-(2-Morpholinoethyl)dibenzo[a,d]cycloheptadiene-5-pyrrolidide (VII).**—A solution of the pyrrolidide (8.3 g., 0.028 mole) in dry toluene (50 ml.) was added to sodium hydride (53.8% dispersion; 1.45 g., 0.032 mole) suspended in toluene (50 ml.). The mixture was stirred and heated under reflux for 4 hr., during which time a precipitate formed and an orange color developed. A solution of 2-chloroethylmorpholine (6.7 g., 0.045 mole) in toluene (50 ml.) was added dropwise and heating was continued for an additional 1 hr. The mixture was filtered while hot and the solution was extracted with dilute hydrochloric acid. The aqueous layer was extracted with ether, made alkaline and the oil was taken up in benzene. Evaporation of the solvent left the

product as a solid; needles from petroleum ether (b.p. 80–100°) or ethyl acetate-hexane, m.p. 148–149° (4.4 g., 38% yield) (see Table II, no. 11A).

**Removal of the Cyano Group.**—A suspension of sodium amide (2.3 g., 0.06 mole) in xylene (100 ml.) was treated with the free base V (5.1 g., 0.015 mole) and the mixture was stirred and heated under reflux for 16 hr. It was cooled, treated with water, and the organic layer was extracted with dilute hydrochloric acid. The acidic layer was made alkaline and the product was collected in benzene. Evaporation of the solvent gave 4.1 g. (87% yield) of IX; the hydrochloride, m.p. 185–187°, was identical with an authentic sample.<sup>2</sup>

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## Some Analogs of Imipramine

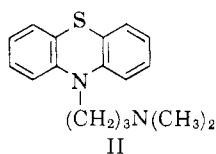
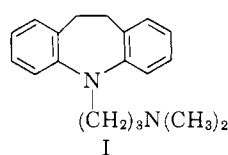
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As part of a search for compounds possessing antidepressant properties, some dialkylaminoalkyl derivatives of 5,6,11,12-tetrahydrodibenz[b,f]azocine, 5-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene and 10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine have been synthesized. A summary of the pharmacological results is given. In various tests for autonomic activity and for antagonism of reserpine effects the N-(3-dimethylaminopropyl) derivatives of the first two ring systems possessed negligible activity, whereas 5-(3-dimethylaminopropyl)-10,11-dihydrodibenzo[b,e][1,4]diazepine showed activity comparable to that of imipramine.

In 1957 it was shown<sup>1</sup> in the Swiss clinics that 5-(3-dimethylaminopropyl)-10,11-dihydrodibenz[b,f]azepine (imipramine) (I) was a useful drug in the treatment of depressive syndromes, and it has since achieved an established position in therapy. It was synthesized<sup>2</sup> initially as an antihistamine, and was tested for tranquillizing properties in view of its close chemical similarity to the phenothiazines. The structural resemblance between imipramine and 10-(3-dimethylaminopropyl)-phenothiazine (promazine) (II), contrasted with their remarkable pharmacological and clinical differences, stimulated speculation on the changes in activity that might be encountered by further changes in the ring system. Häfliger has pointed out<sup>3</sup> that both molecules have similar volume and shape, but that



whereas promazine is a symmetrical molecule, the ring structure of imipramine is asymmetrical, the two aromatic rings being markedly twisted relative to each other. Moreover, with promazine the sulfur atom enables the conjugation of the benzene rings to extend over

this bridge, whereas the two-carbon bridge of imipramine acts as a barrier to conjugation.

With physicochemical points such as these in mind, and with the aim of discovering agents which show modified pharmacological properties compared to imipramine, we have synthesized various derivatives of 5,6,11,12-tetrahydrodibenz[b,f]azocine (V), 5-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XI), and 10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine (XXI). Recently, other groups of workers with presumably the same approach in mind, have described several similar tricyclic systems carrying dialkylaminoalkyl side chains, which are variations of the imipramine and promazine structures. Examples of such compounds are the drug 5-(3-dimethylaminopropylidene)-10,11-dihydrodibenzo[a,d]cycloheptene (amitriptyline),<sup>4</sup> and N-(ω-dialkylaminoalkyl) derivatives of 5,6 dihydro-11H-dibenz[b,e]azepine,<sup>5</sup> 5,10,11,12-tetrahydrodibenz[b,g]azocine,<sup>6</sup> 6,11-dihydrodibenzo[b,e][1,4]thiazepine,<sup>7</sup> and 10,11-dihydrodibenzo[b,f][1,4]thiazepine.<sup>8</sup>

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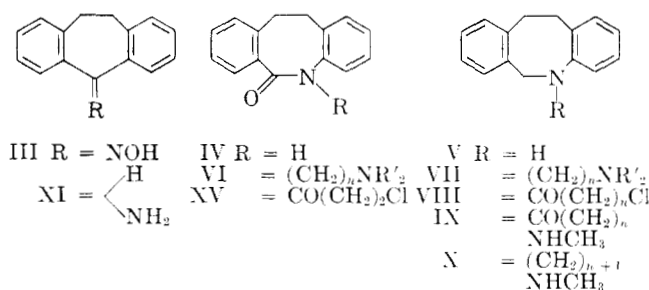
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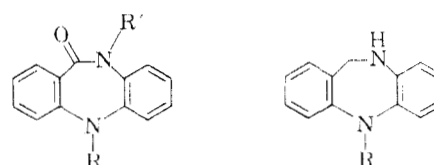
To obtain the dibenzazocine (V), 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-one was converted to the oxime (III), which on Beckmann rearrangement gave the lactam (IV). Subsequent reduction with lithium aluminum hydride afforded the dibenzazocine (V) in 60% over-all yield for the three steps. Alkylations of both the lactam (IV) and the amine (V) to give compounds of the types (VI) and (VII) were performed with the appropriate dialkylaminoalkyl halide in toluene or benzene at reflux temperature in the presence of sodamide.

In the case of compounds possessing monoalkylaminoalkyl side chains, of interest in view of the claimed value<sup>9</sup> of 5-(3-monomethylaminopropyl)-10,11-dihydro-dibenzo[b,f]azepine as an antidepressant, a different reaction sequence was used. The dibenzazocine (V) in tetrahydrofuran was treated with  $\beta$ -chloropropionyl chloride or chloroacetyl chloride, and the corresponding chloroamide (VIII) was almost quantitatively formed. Treatment of these chloro compounds with methylamine in either tetrahydrofuran or benzene gave the aminoamides (IX) which were reduced to the desired diamines (X) with lithium aluminum hydride.

A further series of compounds in which both nitrogen atoms are incorporated in the side chain was derived from 5-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XI). We have noted that in the reduction of an oxime to an amine the use of sodium and ethanol is often superior to that of lithium aluminum hydride, and this was the case with the oxime (III), when sodium and ethanol reduction proceeded in 65% yield. The pure amine was not isolated from a variety of experiments using lithium aluminum hydride. The method described above for the elaboration of the monoalkylaminoalkyl side chain was employed again, both for this purpose and also for the dialkylaminoalkyl series.

For the preparation of compounds of the dibenzodiazepine type (XVIII), the iminolactam (XII) was synthesized by a modification of the literature method.<sup>10</sup> *o*-Bromonitrobenzene and anthranilic acid in amyl alcohol reacted under Ullmann conditions to give N-(*o*-nitrophenyl)anthranilic acid, which was reduced smoothly with stannous chloride to N-(*o*-aminophenyl)anthranilic acid. The latter cyclized on heating in xylene to give the iminolactam (XII) in 83% over-all yield from *o*-bromonitrobenzene. Subsequent acylation with chloroacetyl chloride and  $\beta$ -chloropropionyl chloride gave the chloro compounds (XIII).

This structural assignment, rather than the alternative (XIV), was made on the basis of the infrared absorption of the compounds at 1680 and 1660  $\text{cm}^{-1}$ .



The former band was assigned to the extranuclear carbonyl group and the latter band to the carbonyl group in the ring, as both the parent iminolactam (XII) and benzanilide absorbed at 1660  $\text{cm}^{-1}$ . To support this interpretation, compound XV was prepared by acylation of the dibenzazocinone (IV), and its infrared spectrum was examined. This showed absorption at 1705  $\text{cm}^{-1}$  with a shoulder at 1690  $\text{cm}^{-1}$ , suggesting that acylation of the iminolactam (XII) had indeed given structure XIII and not XIV. The infrared absorption of other semicyclic imides has been reported<sup>11</sup> recently as a doublet occurring in the region 1720–1690  $\text{cm}^{-1}$ .

Treatment of the halo compounds (XIII) with dimethylamine or diethylamine gave the corresponding amines (XVI) in high yield, but the action of methylamine was not so satisfactory. In this case the chloroacetyl compound gave no identifiable product, while the chloropropionyl analog gave a methylamino derivative (XVII), which could only be purified as the hydrochloride.

Treatment of these dialkylamino compounds with lithium aluminum hydride yielded interesting results. The dimethylaminoacetyl compound (XVI,  $n = 1$ ,  $\text{R}'' = \text{CH}_3$ ) in ether solution, underwent hydrogenolysis to give the iminolactam (XII) in poor yield. Cleavages of this type have been reported.<sup>12</sup> The diethylaminopropionyl compound (XVI,  $n = 2$ ,  $\text{R}'' = \text{C}_2\text{H}_5$ ) when reduced in ether gave only the desired diethylaminopropyl compound (XVIIIb) in 52% yield. However, reduction of the dimethylaminopropionyl compound (XVI,  $n = 2$ ,  $\text{R}'' = \text{CH}_3$ ) as a suspension in ether gave two products. The major one was the desired dimethylaminopropyl compound (XVIIIa) (47%) and the lesser product, resulting from only partial reduction, was the lactam (XIX) (4%). In tetrahydrofuran the only product isolated from the reduction was (XVIIIa) in poor yield. Structure XIX, rather than the isomeric amide (XX), was assigned to this compound on the basis of its single infrared band at 1660  $\text{cm}^{-1}$ , which corresponds to the lower frequency band of the two bands observed in the precursor (XVI,  $n = 2$ ,  $\text{R}'' = \text{CH}_3$ ) and is assigned to the ring carbonyl group, as in the case of the chloro compounds (XIII). Furthermore, the ultraviolet spectrum of the compound, like that of the lactam (XII), is virtually identical in

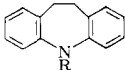
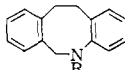
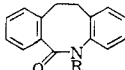
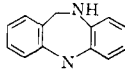
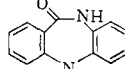
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TABLE I  
 ULTRAVIOLET SPECTRA<sup>a</sup>

Compound	Ref.	$\lambda_{\max}$ in m $\mu$ <sup>b</sup> (molec. extinc. coeff.)
Diphenylamine	13	288 (21,000)
	R = H 13 = (CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub> <sup>c</sup> 3 = COCH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub> 2	290 (20,500) 250 (8,100), 275* (6,300) 222 (10,100), 233* (8,000), 270* (800)
N-Benzylaniline		248 (13,000), 294 (2,200)
	R = H = (CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub> = COCH <sub>2</sub> NHCH <sub>3</sub>	V 244 (8,600), 289 (2,100) VII 260 (5,300) IX 260* (800)
Benzanilide		269 (11,000)
	R = H = (CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub>	IV 270* (1,400) VI 270* (1,000)
<i>o</i> -Aminodiphenylamine	14	238 (9,300), 285 (6,900)
	R = H = (CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub> = (CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub> <sup>d</sup>	XXI 233 (23,200), 299 (15,100) XVIIIa 230 (23,000), 266 (6,500), 309 (4,500) XVIIIa 247 (9,300), 261* (8,200), 290* (3,300)
	R = H <sup>e</sup> = (CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub> <sup>e</sup> = CO(CH <sub>2</sub> ) <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub> <sup>e</sup>	XII 223 (30,200), 255* (17,000), 290* (5,400) XIX 222 (28,700), 245* (18,200), 282* (4,500) XVI 222 (26,500), <sup>f</sup> 270* (6,600)

<sup>a</sup> Unless otherwise mentioned, spectra measured in methanol or 95% ethanol on a Unicam SP500 or Perkin Elmer 137 UV instrument. <sup>b</sup> \* Indicates a shoulder. <sup>c</sup> In water. <sup>d</sup> In 0.01 *N* HCl/MeOH. <sup>e</sup> Spectrum unchanged in 0.01 *N* HCl/MeOH. <sup>f</sup> Not a maximum.

acidic and neutral solution, in contrast to the spectrum of the fully reduced compound (XVIIIa) which shows a distinct change in acidic conditions due to protonation of the cyclic secondary amine (see Table I). Non-aqueous titration measurements of basicity also support these structural assignments.

It is interesting to consider molecular models of the various ring systems in relation to their ultraviolet spectra (see Table I). It has already been observed<sup>13</sup> that the spectrum of 10,11-dihydro-5H-dibenz[b,f]-azepine is very similar to that of diphenylamine, the restricting effect of the ethylene bridge apparently having little effect on the conjugation which exists in diphenylamine. Inspection of a model of the dibenzazocine (V) shows that the nitrogen is still in a configuration which allows considerable resonance with the adjacent benzene ring, and thus the spectrum resembles that of *N*-benzylaniline. In contrast, a model of dibenzazocinone (IV) reveals that, in the configuration most probable for steric reasons, the carbonyl bond is nearly perpendicular to its adjacent ring, and accordingly the conjugation shown by the spectrum of benzanilide is to a large extent lost. The spectrum of the dibenzodiazepine (XXI) is again somewhat similar to diphenylamine, and a comparison with that of *o*-aminodiphenylamine,<sup>14</sup> indicates that in this case the restricting effect of the -CH<sub>2</sub>NH- bridge actually allows better conjugation than in the unbridged analog.

Häfiger has shown<sup>3</sup> that alkylation of 10,11-dihydro-5H-dibenz[b,f]azepine to give imipramine has a hypsochromic effect and also reduces the intensity of the absorption. A parallel effect occurs in alkylation of those ring systems, dibenzazocine (V) and dibenzo-

diazepine (XXI), which still show considerable resonance, whereas alkylation of those ring systems, dibenzazocinone (IV) and dibenzodiazepinone (XII), wherein the conjugation has already been largely destroyed, has little effect on the remaining absorption. Huisgen and co-workers<sup>15</sup> have attributed the hypsochromic effect of *N*-methylation of 10,11-dihydro-5H-dibenz[b,f]azepine to the greater steric interference of the methyl group, compared with a hydrogen atom, in resisting the approach to uniplanarity of the molecule.

The effect of acylation of the various rings is much more dramatic than that of alkylation, due to the competing effect of the normal amide resonance which ob-



viously reduces the availability of the electrons of the nitrogen for conjugation in the ring.<sup>16</sup> This is apparent in the acylation of 10,11-dihydro-5H-dibenz[b,f]azepine (XXI), and dibenzazocine (V), in which extensive loss of conjugation occurs, in contrast to the small loss observed in dibenzodiazepinone (XII).

Since the completion of this work, several of the compounds described by us have appeared in the recent patent literature. Thus dialkylaminoalkyl and related derivatives of 5-amino-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene (IX),<sup>17</sup> and of 10,11-dihydrodibenzo[b,e][1,4]diazepine (XXI)<sup>18</sup> have been described, all with physical constants in agreement with our own. Dialkylaminoalkyl derivatives of the 5,6,11,12-tetra-

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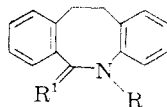
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

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TABLE II  
 N-SUBSTITUTED 5,6,11,12-TETRAHYDRODIBENZ[b,f]AZOCINES


R <sup>1</sup>	R	n <sub>D</sub> <sup>20</sup>	B.p., °C., of base	mm.	Yield, %	Formula	Analyses, %					
							C		H		N	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
O	—(CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub>	1.5744	176–181	0.4	48	C <sub>20</sub> H <sub>24</sub> N <sub>2</sub> O	77.88	77.84	7.84	7.91	9.08	8.89
O	—CH <sub>2</sub> CH <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1.5692	162–166	0.04	57	C <sub>21</sub> H <sub>26</sub> N <sub>2</sub> O	78.22	78.04	8.13	7.92	8.69	8.63
O	—CH <sub>2</sub> CH <sub>2</sub> N 	1.5914	210–216	1	46	C <sub>22</sub> H <sub>26</sub> N <sub>2</sub> O	79.00	79.03	7.84	7.79	8.38	8.65
H <sub>2</sub>	—CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	1.5873	140–146	0.5	41	C <sub>19</sub> H <sub>24</sub> N <sub>2</sub>	81.38	81.67	8.63	8.26	9.99	9.88
H <sub>2</sub>	—CH <sub>2</sub> CH <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	1.5732	140–144	0.2	68	C <sub>21</sub> H <sub>26</sub> N <sub>2</sub>	81.77	81.68	9.15	8.78	9.08	9.35
H <sub>2</sub>	—(CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub>	1.5802	163–168	1.4	70	C <sub>20</sub> H <sub>26</sub> N <sub>2</sub>	81.58	81.94	8.90	8.94	9.52	9.27
H <sub>2</sub>	—CH <sub>2</sub> CH <sub>2</sub> N 	1.5857	180–184	0.05	56	C <sub>22</sub> H <sub>26</sub> N <sub>2</sub>	82.45	83.00	8.81	8.97	8.74	8.74

hydrodibenz[b,f]azocine (V)<sup>19</sup> and of 10,11-dihydro-5H-dibenzo[b,e][1,4]diazepine-11-one (XII),<sup>20</sup> the latter having the side chain in the 10-position, also have been reported recently.

### Experimental

Melting points were taken on an Electrothermal melting point apparatus, Series 1A and are corrected. Infrared spectra were determined on a Perkin-Elmer Infracord 137 instrument, solids as Nujol mulls and liquids as thin films.

**10,11-Dihydrodibenzo[a,d]cyclohepten-5-one Oxime (III).**—10,11-Dihydrodibenzo[a,d]cyclohepten-5-one<sup>21</sup> (150 g.), and hydroxylamine hydrochloride (150 g.), in pyridine (2.25 l.), were heated under reflux for 24 hr. The bulk of the pyridine was removed under reduced pressure and the residue was poured into water which was then extracted with ether. After washing the extracts with dilute hydrochloric acid, bicarbonate solution and water, the solvent was removed to leave a solid (150 g.), m.p. 153–164°. Recrystallization from benzene–light petroleum afforded the pure oxime, m.p. 166–169°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>NO: C, 80.69; H, 5.87; N, 6.28. Found: C, 80.69; H, 5.88; N, 5.82.

**5,6,11,12-Tetrahydrodibenz[b,f]azocin-6-one (IV).** The oxime III (12 g.), dissolved in ether (300 ml.), was treated with phosphorus pentachloride (25 g.) at room temperature. A solid initially precipitated but redissolved during the course of the reaction which was allowed to proceed for 14 hr. Water (300 ml.) was then added cautiously, the organic layer was washed with bicarbonate solution and water, dried and the solvent removed. The residual solid, m.p. 239–247°, was recrystallized from aqueous acetone to afford the pure lactam (8.6 g.), m.p. 250–252°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>NO: C, 80.69; H, 5.87; N, 6.28. Found: C, 80.72; H, 5.66; N, 6.48; infrared spectrum  $\nu_{\max}$  3200, 1650 cm.<sup>-1</sup>.

**5,6,11,12-Tetrahydrodibenz[b,f]azocine (V).**—The lactam IV (40.0 g.) in anhydrous ether (4 l.) was heated under reflux for 5 hr. with lithium aluminum hydride (20 g.). The excess hydride was decomposed under nitrogen by cautious addition of water (20 ml.). Sodium hydroxide solution (15%, 20 ml.) then water (80 ml.) were added to facilitate the removal of inorganic salts by filtration. The ether solution was washed with water and dried, and removal of the solvent left the white crystalline amine (36 g.), m.p. 125–132°. Recrystallization from ethanol gave the analytical sample, m.p. 130–132°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>13</sub>N: C, 86.08; H, 7.22; N, 6.70. Found: C, 85.86; H, 7.12; N, 7.10.

**Alkylation of the Dibenzazocines (IV) and (V).**—Sodamide (1 equiv.) in benzene or toluene was stirred at reflux with 0.9 equiv. of the dibenzazocine for 0.5 to 2 hr. After addition of 1.2 equiv. of the dialkylaminoalkyl chloride, stirring at reflux was con-

tinued for 4–18 hr. Water was added and the organic layer was extracted with dilute hydrochloric acid. The acidic solution was basified and extracted with ether. The residue obtained following removal of ether was distilled. Table II lists the compounds prepared in this manner.

**5-(3-Chloropropionyl)-5,6,11,12-tetrahydrodibenz[b,f]azocine (VIII, n = 2).**—The dibenzazocine V (5 g.) in tetrahydrofuran (40 ml.) and triethylamine (3 ml.) was treated dropwise with  $\beta$ -chloropropionyl chloride (4 g.) in tetrahydrofuran (25 ml.). The mixture was heated under reflux for 1 hr., water (100 ml.) was added, and the organic solvents were removed under reduced pressure. The resulting solid was collected by filtration and was recrystallized from 2-propanol to give 4.6 g., m.p. 89–92°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>18</sub>ClNO: C, 72.13; H, 5.99; Cl, 11.85; N, 4.67. Found: C, 72.12; H, 5.76; Cl, 11.76; N, 4.80.

The corresponding **chloroacetyl compound (VIII, n = 1)** was prepared similarly, m.p. 113–116°.

*Anal.* Calcd. for C<sub>17</sub>H<sub>16</sub>ClNO: C, 71.45; H, 5.60; Cl, 12.44; N, 4.90. Found: C, 71.07; H, 5.37; Cl, 12.40; N, 4.92;  $\nu_{\max}$  1670 cm.<sup>-1</sup>.

Acylation of the dibenzazocinone (IV) in an identical manner yielded the **5-(3-chloropropionyl) derivative (XV)** (from ethanol), m.p. 124–126°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>16</sub>ClNO<sub>2</sub>: C, 68.91; H, 5.14; N, 4.43. Found: C, 68.73; H, 5.09; N, 4.49;  $\nu_{\max}$  1705 cm.<sup>-1</sup>, with a shoulder at 1690 cm.<sup>-1</sup>.

**5-(3-Methylaminopropionyl)-5,6,11,12-tetrahydrodibenz[b,f]azocine (IX, n = 2).**—Methylamine was passed through a solution of the chloro compound (VIII, n = 2) (5.5 g.) in tetrahydrofuran (150 ml.) for 2.5 hr. and the mixture was left to stand overnight. A quantity of methylamine hydrochloride precipitated during the reaction and was removed by filtration. Dilute hydrochloric acid was added to the filtrate and the resulting mixture was treated with ether. The acidic solution was basified and extracted with ether. The extracts were washed with water, dried and the solvent was removed to leave an oil (5.5 g.). This was dissolved in a minimum of absolute ethanol and treated with ethereal hydrogen chloride, when the hydrochloride was precipitated. Recrystallization from 2-propanol gave the pure compound (4.29 g.), m.p. 219–221°.

*Anal.* Calcd. for C<sub>19</sub>H<sub>22</sub>ClN<sub>2</sub>O: C, 69.00; H, 6.96; Cl, 10.75; N, 8.47. Found: C, 69.07; H, 6.85; Cl, 10.56; N, 8.57.  $\nu_{\max}$  2450, 1650 cm.<sup>-1</sup>.

The related **methylaminoacetyl compound (IX, n = 1)** was prepared similarly as the hydrochloride, m.p. 238–241°.

*Anal.* Calcd. for C<sub>18</sub>H<sub>21</sub>ClN<sub>2</sub>O: C, 68.25; H, 6.63; Cl, 11.21; N, 8.85. Found: C, 68.10; H, 6.82; Cl, 11.05; N, 8.56.

**5-(3-Methylaminopropyl)-5,6,11,12-tetrahydrodibenz[b,f]azocine (X, n = 2).**—The amino amide (IX, n = 2) (15 g.) in ether (100 ml.) was treated portionwise with a suspension of lithium aluminum hydride (6 g.) in ether (50 ml.) and the resulting mixture was heated under reflux for 3 hr. Addition of water (6 ml.), 15% sodium hydroxide solution (6 ml.) and a further amount of water (24 ml.) rendered the inorganic salts easily removable by filtration. The ether solution was dried and a colorless oil was obtained after removal of solvents. Distillation gave the pure product, 8.4 g., b.p. 156–159° (0.02 mm.),  $n_D^{20}$  1.5905.

(19) Koninklijke Pharm., Belgian Patent 616,983 (April 27, 1961).

(20) J. Davoll and H. Davies, S. Afr. Patent R61/2994 (December 23, 1960).

(21) A. C. Cope and S. W. Fenton, *J. Am. Chem. Soc.*, **73**, 1673 (1951).

*Anal.* Calcd. for  $C_{19}H_{24}N_2$ : C, 81.38; H, 8.63; N, 9.99. Found: C, 81.21; H, 8.77; N, 9.75.

The corresponding **methylaminoethyl compound (X,  $n = 1$ )** was similarly prepared, b.p. 141–145° (0.05 mm.),  $n_D^{20}$  1.5944.

*Anal.* Calcd. for  $C_{19}H_{22}N_2$ : C, 81.16; H, 8.33; N, 10.52. Found: C, 81.29; H, 8.23; N, 10.04.

**5-Amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XI).**—A solution of the oxime III (2 g.) in absolute ethanol (100 ml.) was heated under reflux while sodium (12 g.) was added in small portions over 1.5 hr. When all the sodium had dissolved, water (300 ml.) was added and the cloudy mixture was extracted with ether. The extracts were dried and removal of solvent afforded a solid (1.8 g.). Two recrystallizations from 2-propanol gave pure material, 1.2 g., m.p. 91–93° (lit.<sup>17</sup> m.p. 91–92°).

*Anal.* Calcd. for  $C_{16}H_{15}N$ : C, 86.08; H, 7.22; N, 6.69. Found: C, 86.40; H, 7.07; N, 6.55.

**5-Chloroacetamido-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XXIIa).**—Chloroacetyl chloride (3.4 g.) in tetrahydrofuran (10 ml.) was added slowly to a solution of the amine (IX) (4.2 g.) in tetrahydrofuran (25 ml.) and triethylamine (2.1 g.) and the mixture was allowed to stand overnight. Water was added and the precipitated solid was collected and dried (5.1 g.), m.p. 224–229°. The analytical sample, m.p. 233–237°, was obtained from ethanol (lit.<sup>17</sup> m.p. 227–229°).

*Anal.* Calcd. for  $C_{17}H_{16}ClNO$ : C, 71.45; H, 5.6; Cl, 12.44; N, 4.90. Found: C, 71.41; H, 5.51; Cl, 12.68; N, 5.13;  $\nu_{max}$  3400, 1670  $cm^{-1}$ .

The corresponding **3-chloropropionyl compound (XXIIb)** was prepared by a similar procedure, m.p. 230–233°.

*Anal.* Calcd. for  $C_{18}H_{18}ClNO$ : C, 72.13; H, 6.01; Cl, 11.85; N, 4.67. Found: C, 72.41; H, 5.98; Cl, 12.19; N, 4.87.

**5-Methylaminoacetamido-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XXIIIa).**—Methylamine was bubbled through a solution of the chloroacetamido compound (XXIIa) (2 g.) in tetrahydrofuran (60 ml.) for 8 hr. and the mixture was allowed to stand overnight. The solution was acidified with dilute hydrochloric acid and the solids thereby precipitated were collected, washed with water and dried. Recrystallization from 2-propanol afforded the pure hydrochloride (1.98 g.), m.p. 286–290°.

*Anal.* Calcd. for  $C_{18}H_{21}ClN_2O$ : C, 68.25; H, 6.63; N, 8.85. Found: C, 68.62; H, 6.86; N, 9.03.

The **methylaminopropionyl derivative (XXIIIb)**, was prepared similarly (as the hydrochloride, m.p. 229–232°).

*Anal.* Calcd. for  $C_{19}H_{23}ClN_2O$ : C, 68.70; H, 6.84; N, 8.28. Found: C, 68.42; H, 6.91; N, 8.14.

**5-Dimethylaminoacetamido-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XXIV).**—The chloroacetamido compound (XXIIa) (6 g.) was dissolved in dimethylformamide (80 ml.) containing dimethylamine (10 ml.) and the resulting solution was heated under reflux for 4 hr. Solvent was removed under reduced pressure and the residue was taken into ether and washed with dilute sodium hydroxide solution. Removal of ether afforded the crystalline amino amide which was recrystallized from 2-propanol to afford the pure product (5.14 g.), m.p. 156–160° (lit.<sup>17</sup> m.p. 153–154°).

*Anal.* Calcd. for  $C_{19}H_{22}N_2O$ : C, 77.52; H, 7.53; N, 9.52. Found: C, 77.34; H, 7.57; N, 9.67.

**5-Methylaminoethylamino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XXVa).**—The methylaminoacetyl compound (XXIIIa) (6 g.) suspended in ether (120 ml.) was treated with lithium aluminum hydride (3 g.) and the mixture heated under reflux for 8 hr. The product, a colorless oil (5.68 g.), was isolated in the usual manner. It was taken into ether and treated with ethereal hydrogen chloride, when the dihydrochloride precipitated. This material was collected and recrystallized from ethanol to give the pure material (3.6 g.), m.p. 214–217°.

*Anal.* Calcd. for  $C_{18}H_{24}Cl_2N_2$ : C, 63.72; H, 7.13; Cl, 20.89; N, 8.26. Found: C, 64.09; H, 7.12; Cl, 20.19; N, 8.24.

By identical procedures **5-(3-methylaminopropylamino)-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XXVb)** was prepared as the dihydrochloride, m.p. 222–226°.

*Anal.* Calcd. for  $C_{19}H_{26}Cl_2N_2$ : C, 64.59; H, 7.37; Cl, 20.11; N, 7.93. Found: C, 64.63; H, 7.20; Cl, 19.19; N, 7.65.

Similarly, **5-dimethylaminoethylamino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (XXVI)** was prepared as the dihydrochloride, m.p. 192–195° (lit.<sup>17</sup> m.p. 178–180°), by reduction of (XXIV).

*Anal.* Calcd. for  $C_{19}H_{28}Cl_2N_2$ : C, 64.59; H, 7.37; Cl, 20.11; N, 7.93. Found: C, 64.44; H, 7.47; Cl, 20.04; N, 7.62.

**N-(o-Nitrophenyl)-anthranilic acid.**—o-Bromonitrobenzene (100

g.), anthranilic acid (100 g.), anhydrous potassium carbonate (100 g.), and activated copper bronze<sup>22</sup> in amyl alcohol (400 ml.) were brought cautiously to reflux with stirring. After 30 min. the mixture set solid. It was heated for a further 30 min., 250 ml. of water was added and the mixture steam distilled to remove amyl alcohol and unchanged o-bromonitrobenzene. When cool, the residue was acidified with hydrochloric acid (20%) to pH 6, and the acid filtered off. A dried sample had m.p. 208–212° (lit.<sup>10</sup> m.p. 219°).

**N-(o-Aminophenyl)anthranilic Acid.**—Crude N-(o-nitrophenyl)anthranilic acid was added to a mixture of stannous chloride dihydrate (680 g.), concd. hydrochloric acid (680 ml.) and ethanol (2.5 l.), and the stirred suspension was heated on the steam bath until the acid had dissolved, and the pale complex had commenced to crystallize (ca. 1 hr.). When cold, the solid was collected and dissolved in concd. aqueous ammonia. After making the volume up to 3 l. with water, the mixture was acidified with hydrochloric acid (5 N) to pH 6. The product was filtered off and used directly in the next step. A dried sample had m.p. 206–211°.

**10,11-Dihydrodibenzo[b,e][1,4]diazepin-11-one (XII).**—The crude acid (m.p. 206–211°) was heated under reflux in xylene (2 l.) for 48 hr. with continuous removal of water. The dark green product crystallized out during the cyclization and, when cold, it was filtered off. It had m.p. 257–262° dec. (lit.<sup>10</sup> m.p. 250°),  $\nu_{max}$  3400, 3230, 1660  $cm^{-1}$ . In several runs the best over-all yield from o-bromonitrobenzene was 83%.

**5-(3-Chloropropionyl)-10,11-dihydrodibenzo[b,e][1,4]diazepin-11-one (XIII,  $n = 2$ ).**—The diazepinone XII (18 g.), 3-chloropropionyl chloride (20 ml.) and N,N-dimethylaniline (6 g.) in dry tetrahydrofuran (400 ml.) were heated under reflux for 5 hr. The product was isolated by pouring the reaction mixture into an excess of 5% potassium bicarbonate and collecting the precipitated solid (95% yield), m.p. 212–214°. The analytical specimen (from methanol) had m.p. 219°.

*Anal.* Calcd. for  $C_{18}H_{15}ClN_2O$ : C, 63.90; H, 4.36; Cl, 11.79; N, 9.32. Found: C, 63.79; H, 4.52; Cl, 11.52; N, 9.19;  $\nu_{max}$  3230, 1680, 1660  $cm^{-1}$ .

In a similar manner was prepared the **chloroacetyl compound (XIII,  $n = 1$ )** (68%), m.p. 239–241°.

*Anal.* Calcd. for  $C_{18}H_{17}ClN_2O_2$ : C, 62.85; H, 3.87; Cl, 12.37. Found: C, 63.29; H, 3.70; Cl, 12.51.

**Reaction of Chloroacetyl Compounds (XIII) with Amines.**  
**5-(3-Dimethylaminopropionyl)-10,11-dihydrodibenzo[b,e][1,4]diazepin-11-one (XVI,  $n = 2$ ,  $R' = CH_3$ ).**—The chloropropionyl compound (XIII,  $n = 2$ ) (7.9 g.) and dimethylamine (10 ml.) were stirred at room temperature in acetone (200 ml.) for 22 hr. After evaporation to dryness the residue was dissolved in 5 N hydrochloric acid, washed with chloroform, and basified with potassium hydroxide pellets. Extraction with chloroform, drying and evaporation yielded the product (78%), which was recrystallized from ethanol. It had m.p. 184–190°.

*Anal.* Calcd. for  $C_{18}H_{19}N_3O_2$ : C, 69.88; H, 6.19; N, 13.58. Found: C, 70.10; H, 6.43; N, 13.34;  $\nu_{max}$  1680, 1660  $cm^{-1}$ .

In a similar manner, using either dimethylamine or diethylamine in ethanol, under reflux for 18 hr., there were prepared:

**5-(3-Diethylaminopropionyl)-10,11-dihydrodibenzo[b,e][1,4]diazepin-11-one (XVI,  $n = 2$ ,  $R' = C_2H_5$ )** (from acetone), m.p. 128–129°.

*Anal.* Calcd. for  $C_{20}H_{23}N_3O_2$ : C, 71.19; H, 6.87; N, 12.45. Found: C, 71.29; H, 6.58; N, 12.68.

**5-Dimethylaminoacetyl-10,11-dihydrodibenzo[b,e][1,4]diazepin-11-one (XVI,  $n = 1$ ,  $R' = CH_3$ )** (from acetone), m.p. 170–173°.

*Anal.* Calcd. for  $C_{17}H_{17}N_3O_2$ : C, 69.13; H, 5.80; N, 14.23. Found: C, 69.09; H, 5.71; N, 14.10.

**5-Diethylaminoacetyl-10,11-dihydrodibenzo[b,e][1,4]diazepin-11-one (XVI,  $n = 1$ ,  $R' = C_2H_5$ )** (from acetone and ethanol), m.p. 145–146°.

*Anal.* Calcd. for  $C_{19}H_{21}N_3O_2$ : C, 70.56; H, 6.55; N, 13.00. Found: C, 70.99; H, 6.33; N, 12.90.

**5-(3-Methylaminopropionyl)-10,11-dihydrodibenzo[b,e][1,4]diazepin-11-one (XVII).**—Methylamine was bubbled into a solution of the chloropropionyl compound (XIII,  $n = 2$ ) (3 g.) in tetrahydrofuran (100 ml.) under gentle reflux, until no more solid was precipitated (9–12 hr.). The mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in

(22) A. I. Vogel, "Practical Organic Chemistry," Longmans, London (1956), p. 192.

absolute ethanol and treated with ethereal hydrogen chloride. Excess ether was added to complete precipitation of the hydrochloride (2.8 g.). This was recrystallized from ethanol, and had m.p. 255–257°.

*Anal.* Calcd. for  $C_{17}H_{18}ClN_3O_2$ : C, 61.54; H, 5.47; N, 12.66. Found: C, 60.89; H, 5.31; N, 12.55.

**5-(3-Dimethylaminopropyl)-10,11-dihydrodibenzo[b,e][1,4]-diazepine (XVIIIa).**—To a clear stirred solution of lithium aluminum hydride (15 g.) in dry ether (1 l.) under nitrogen was added in portions the 3-dimethylaminopropionyl compound (XVI,  $n = 2$ ,  $R'' = CH_3$ ) (44 g.). The suspension was stirred and heated under reflux for 7 hr. and after stirring at room temperature for 10 hr., was worked up by the successive cautious addition of ethyl acetate (25 ml.), water (15 ml.), 15% sodium hydroxide (15 ml.) and water (45 ml.). The inorganic solids were filtered off, washed with ether, and evaporation of the combined filtrate and washings yielded an oily residue, which crystallized from low boiling petroleum ether-ether (1:1, 50 ml.) to give the product (17.5 g., 47%), m.p. 101–104° (lit.<sup>18</sup> m.p. 99–101°).

*Anal.* Calcd. for  $C_{18}H_{23}N_3$ : C, 76.83; H, 8.24; N, 14.93. Found: C, 76.41; H, 8.10; N, 14.68.

On standing for several days, the mother liquors of the above crystallization deposited further material, which was filtered off and recrystallized from acetone to give **5-(3-dimethylaminopropyl)-10,11-dihydrodibenzo[b,e][1,4]diazepin-11-one (XIX)** (1.6 g., 4%), m.p. 147–149° (lit.<sup>23</sup> m.p. 141–144°).

*Anal.* Calcd. for  $C_{18}H_{21}N_3O$ : C, 73.19; H, 7.17; N, 14.23. Found: C, 72.97; H, 7.37; N, 14.12.

The infrared spectrum showed a single C=O band at 1660  $cm^{-1}$ .

**5-(3-Diethylaminopropyl)-10,11-dihydrodibenzo[b,e][1,4]diazepine (XVIIIb).**—This was prepared in an identical manner by lithium aluminum hydride reduction in ether of the diethylaminopropionyl compound (XVI,  $n = 2$ ,  $R'' = C_2H_5$ ). It was recrystallized from ethyl acetate, m.p. 84°, yield 52%.

*Anal.* Calcd. for  $C_{20}H_{27}N_3$ : C, 77.62; H, 8.80; N, 13.58. Found: C, 77.53; H, 8.83; N, 13.37.

Attempted reductions with lithium aluminum hydride of 5-(3-methylaminopropionyl)-, and dimethylaminoacetyl-10,11-dihydrodibenzo[b,e][1,4]diazepin-11-one gave in the former case no identifiable product, and in the latter case a small quantity of 10,11-dihydrodibenzo[b,e][1,4]diazepine-11-one only was isolated.

**10,11-Dihydrodibenzo[b,e][1,4]diazepine (XXI)** was prepared in the same manner by reduction with lithium aluminum hydride in tetrahydrofuran of the iminolactam XII. The crude product (86%) obtained by trituration with ether, could be recrystallized from benzene to give the analytical specimen, m.p. 196–203°.

*Anal.* Calcd. for  $C_{13}H_{12}N_2$ : C, 79.56; H, 6.16. Found: C, 79.09; H, 6.03;  $\nu_{max}$  3330  $cm^{-1}$ .

## Pharmacology

**Experimental Methods.**—In the absence of any laboratory test which may be considered specific for the clinical antidepressant activity of imipramine-like drugs, compounds were examined in a number of animal tests designed to assess effects upon a wide range of autonomic mechanisms and to demonstrate antagonism of various actions of reserpine. In each test imipramine served as the reference standard drug.

For antagonism to reserpine, the compounds were tested for their reversal of reserpine-induced ptosis in rabbits,<sup>24</sup> shortening of alcohol sleep induced in mice by reserpine (a modification of the method of Sulser, Watts, and Brodie<sup>25</sup>) and antagonism of reserpine bradycardia in rats. In the last-mentioned method, rats were anesthetized with allobarbitol-urethane after reserpine (5 mg./kg. i.p.) 18 hr. previously, and their heart-rates measured by means of a 2 channel pen-recording oscillograph for 1 hr. before and 5 hr. after injection of the imipramine-like drug. The minimum dose of imipramine-like drug to produce a marked reversal of the bradycardia was ascertained.

For assessing the autonomic effects of the compounds, they were examined for their potentiation of the actions of the following agents believed to act upon adrenergic mechanisms: norepinephrine (pressor effect in dog under pentobarbital sodium), amphet-

Antagonism to reserpine	1	1.5	1	>50	>50
Bradycardia, rat, min. ED, s.c.	13	7	11	22	11
Ptosis, rabbit, min. ED, i.v.	80	10	30	>50	30
Prolongation of alcohol sleep, mouse, ED <sub>50</sub> p.o.	0.1	0.1	0.1	0.1	0.1
Potentialiation of adrenergic agents	4	9	>50	36	>50
Norepinephrine, dog, min. ED i.v.	6	2.5	>50	>50	>50
Amphetamine, rat, ED <sub>50</sub> p.o.	1–2	0.1	>2	>5	>50
Yohimbine, mouse, ED <sub>50</sub> p.o.	31	12	>50	>50	>50
Tranquillizing or sympatholytic activity	50	19	>50	>50	>50
Block of carotid occlusion reflex, dog, min. ED, i.v.					
Prolongation of alcohol sleep, mouse, min. ED, p.o.					
Parasympatholytic activity, mydriasis, mouse, ED <sub>50</sub> p.o.					

(23) Wander S. A., French Patent M.911 (September 22, 1959).

(24) D. Maxwell and H. Palmer, *Nature*, **191**, 84 (1961).

(25) F. Sulser, J. Watts, and B. B. Brodie, *Federation Proc.*, **19**, 268 (1960).

<sup>a</sup> Imipramine HCl. <sup>b</sup> Higher doses produce bradycardia.

amine (excitation in rats<sup>26</sup>) and yohimbine (toxicity in mice<sup>27</sup>). 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<sup>28</sup>). 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 leucocytopenia 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.

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(28) P. Pulewka, *Arch. Exp. Pathol. Pharmacol.*, **168**, 307 (1932).

## Quinazolines and 1,4-Benzodiazepines. X.<sup>1</sup> Nitro-Substituted 5-Phenyl-1,4-benzodiazepine Derivatives<sup>2</sup>

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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 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  $\alpha$ -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-2H-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-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 1) consisted of treating the bromoacetamido derivatives II(a,b,c,e) (Table I) of the known amino-

nitrobenzophenones I(a,b,c,e)<sup>3</sup> with ammonia and cyclizing the products III to the benzodiazepinones IV using essentially the procedures described previously.<sup>4</sup> 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-2H-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).