g (0.044 mol, 79%) of the product; pure in TLC.

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# *Notes*

## Electronic Factors in the Structure–Activity Relationship of Some 1,4-Benzodiazepin-2-ones

T. Blair and G. A. Webb*

*Department of Chemical Physics, University of Surrey, Guildford, Surrey, England.* *Received January 17, 1977*

Some significant correlations are observed between the CNS activities of a series of 59 benzodiazepines and some calculated electronic indices. The parameters concerned are the net charge on the carbonyl oxygen atom of the lactam ring and the total molecular dipole moment, correlations with the latter index being superior. The utility of the observed relationships is discussed.

It has been widely proposed[1–5] that geometrical factors play a major part in determining the chemical reactivity, and resultant pharmacological activity, of compounds containing lactam rings. The degree of nonplanarity of the amide group is thought to determine the lability of the lactam ring. However, if the geometry of the lactam ring remains essentially constant in a series of compounds then it is probable that electronic factors play an important role. This has been observed in a series of nine *N*-phenyl β-lactams with various phenyl substituents.[6] A good correlation is reported between rate constants for base hydrolysis of the amide linkage and Hammett substituent parameters.[6]

The 1,4-benzodiazepin-2-ones are a series of lactams including the clinically employed drugs diazepam, nitrazepam, oxazepam, and fluroazepam.[7] Although several empirical rules have been observed for the molecular design of these lactams with high central nervous system (CNS) activity,[8] so far no mechanistic rationale has been provided to account for these rules.

We report the results of some CNDO/2 molecular orbital calculations on 59 substituted 1,3-dihydro-2*H*-1,4-benzadiazepin-2-ones with a view to finding the electronic quantities most relevant to drug activity. The calculations are based upon atomic coordinates obtained from the crystal structure of diazepam (1-methyl-5-phenyl-7-chloro-1,3-dihydro-2*H*-benzodiazepin-2-one).[9] It is assumed that the placement and alteration of substituents does not affect the skeletal structure of the molecule. In the present context this is perhaps most tenuous for the replacement of the 1-methyl group by hydrogen (Chart I), since slight changes of lactam ring geometry are probably very critical to reactivity.[1–5]

### Results and Discussion

CNDO/2 calculations were performed on a series of 25 substituted 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones with a variety of substituents in the 7 and 2′ positions (Chart

I). Some charge densities, $q$, and dipole moments, $\mu$, are reported in Table I. The drug activities[8] are expressed as log $1/C$, where $C$ is the concentration in mmol/kg required to elicit a defined response in 50% of a sample of treated animals. These values were obtained from the results of four of the screening methods described in ref 8. The same abbreviations are used here as in ref 8: inclined screen (IS), a measure of muscle relaxant activity in mice; footshock (FS), a measure of taming activity in mice; Met (pentylenetetrazole test), a measure of anticonvulsant activity in mice; Cat., a measure of sedation and muscle relaxation in cats.

The correlation coefficients and $t$ values for the slopes of the regression lines[15] of each drug activity on each CNDO quantity are presented in Table II. It may be seen from Table II that for each drug activity, the only regressions which are significant at the 0.1% level are those on $q_0$ and $\mu$.

Positive correlations with net atomic charges for compounds 1–25 might have been expected from the observation that drug activity increases with the electron-withdrawing nature of the substituents in the 7 and 2′ positions of rings A and C, respectively. However, for substitutions elsewhere on these rings, the situation is more complex.[8]

For ring A, shifting the electron-withdrawing substituent from position 7 to any other position on this ring greatly reduces the activity, and the addition of any substituent elsewhere in addition to $R_7$ also reduces activity.

For ring C, a similar situation arises, since the placement of any substituent in the meta position (3′) reduces activity, so to a greater extent does the placement of a substituent in the para position (4′). It is impossible to give any rationale for these effects in terms of empirical Hammett-type substituent constants.

If either $q_0$ or $\mu$ is, or is firmly correlated to, a uniquely causal quantity, then it should be expected that its correlation with drug activity should survive the type of changes in rings A and C described above. With this test in mind, the CNDO studies were extended to include compounds numbered 26–59 in Table III. This list includes, as well as compounds with varied positions and types of ring A and ring C substituents, four compounds with a pyridyl instead of phenyl substituent in position 5 of ring B. In these four cases, a minimum energy dihedral angle for the pyridyl ring with respect to ring B was used. This geometry optimization gave a conformation twisted by about 80° from the x-ray conformation of ring C.

The following regressions were obtained (standard errors are given in parentheses) for each type of drug activity on $q_0$ and $\mu$, separately and combined, for all compounds in Tables I and III active in that test.

inclined screen (45 active compounds)

$$\log 1/C = 57.2\ (\pm 24.2)\ q_0 + 19.9\ (\pm 8.2) \quad (1a)$$

$r = 0.3392$, $s = 0.5809$, $F = 5.59$

$$\log 1/C = -0.316\ (\pm 0.047)\ \mu + 1.62\ (\pm 0.15) \quad (1b)$$

$r = 0.7190$, $s = 0.4292$, $F = 46.01$

$$\log 1/C = 22.3\ (\pm 18.7)\ q_0 - 0.298\ (\pm 0.048)\ \mu + 9.1\ (\pm 6.3) \quad (1c)$$

$r = 0.7299$, $s = 0.4271$, $F = 23.95$

footshock (39 active compounds)

$$\log 1/C = 112.8\ (\pm 22.2)\ q_0 + 39.5\ (\pm 7.5) \quad (2a)$$

$r = 0.6406$, $s = 0.4458$, $F = 25.76$

$$\log 1/C = -0.339\ (\pm 0.049)\ \mu + 2.21\ (\pm 0.15) \quad (2b)$$

$r = 0.7476$, $s = 0.3856$, $F = 46.88$

$$\log 1/C = 22.1\ (\pm 31.9)\ q_0 - 0.293\ (\pm 0.082)\ \mu + 9.57\ (\pm 10.6) \quad (2c)$$

$r = 0.7515$, $s = 0.3883$, $F = 23.35$

Met (52 active compounds)

$$\log 1/C = 134.4\ (\pm 38.5)\ q_0 + 47.3\ (\pm 13.0) \quad (3a)$$

$r = 0.4430$, $s = 0.9905$, $F = 12.21$

$$\log 1/C = -0.500\ (\pm 0.089)\ \mu + 3.26\ (\pm 0.29) \quad (3b)$$

$r = 0.6206$, $s = 0.8663$, $F = 31.32$

$$\log 1/C = 24.9\ (\pm 43.8)\ q_0 - 0.4583\ (\pm 0.12)\ \mu + 11.6\ (\pm 14.6) \quad (3c)$$

$r = 0.6238$, $s = 0.8723$, $F = 15.61$

Cat. (39 active compounds)

$$\log 1/C = 145.4\ (\pm 27.3)\ q_0 + 52.2\ (\pm 9.3) \quad (4a)$$

$r = 0.6581$, $s = 0.5638$, $F = 28.26$

$$\log 1/C = -0.481\ (\pm 0.067)\ \mu + 4.24\ (\pm 0.19) \quad (4b)$$

$r = 0.7614$, $s = 0.4855$, $F = 51.03$

$$\log 1/C = 42.2\ (\pm 35.9)\ q_0 - 0.389\ (\pm 0.103)\ \mu + 18.3\ (\pm 11.9) \quad (4c)$$

$r = 0.7715$, $s = 0.4830$, $F = 26.47$

It may be seen that there is a general decline in correlation on inclusion of the data in Table III. Regressions (1a) and (3a) on $q_0$ above are no longer significant at the 0.1% level. However, all regressions on $\mu$ alone retain high significance, indicating that this quantity is, or is more closely correlated to, a causal quantity. The improvement in regressions on $\mu$ brought about by introducing $q_0$ as well [as in (1c), (2c), (3c), and (4c)] is generally not very significant, because of considerable covariance between $q_0$ and $\mu$.

The introduction of the Hansch lipophilic substituent constant[16] into each of the regressions in no case produced a significant improvement.

It is a frequent criticism of this type of drug activity regression analysis that it does not take into account wholly inactive compounds. For the case in hand, the assessment of drug activity involved step by step increases in administered dosage. If the compound failed to elicit the required response by the time that a certain arbitrary dose had been reached, administration was discontinued and the compound labeled "inactive".[8]

Chart I. Structure of Some Substituted 1,3-Dihydro-2*H*-1,4-benzodiazepin-2-ones

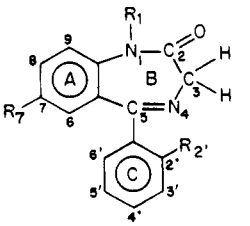

Table I. Drug Activities and CNDO Data for Some 2',7-Disubstituted 1,4-Benzodiazepin-2-ones

| No. | Substituents $R_1$ | $R_7$ | $R_{2'}$ | Drug activities[a] IS[b] | FS[c] | Met[d] | Cat.[e] | Lactam ring atomic charges $q_{N_1}$ | $q_{C_2}$ | $q_{C_3}$ | $q_{N_4}$ | Carbonyl oxygen charge $q_O$ | Dipole moment $\mu$ (Debye) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | H | H | H | 0.1968 | 0.3729 | Inactive | Inactive | −0.2097 | +0.3491 | +0.0161 | −0.1652 | −0.3431 | 5.1398 |
| 2 | H | F | H | 0.2287 | 0.4048 | Inactive | 1.8028 | −0.2082 | +0.3489 | +0.0156 | −0.1598 | −0.3414 | 3.6473 |
| 3 | H | Cl | H | 0.5570 | 1.1311 | 1.6539 | 2.4321 | −0.2083 | +0.3500 | +0.0155 | −0.1618 | −0.3389 | 3.0260 |
| 4 | H | CN | H | 0.5416 | 0.8146 | 2.3027 | 2.7177 | −0.2090 | +0.3495 | +0.0157 | −0.1631 | −0.3398 | 2.8087 |
| 5 | H | $NO_2$ | H | 1.2726 | 1.7497 | 2.7497 | 3.4487 | −0.2089 | +0.3501 | +0.0150 | −0.1579 | −0.3333 | 1.7571 |
| 6 | H | $CF_3$ | H | 1.4829 | 1.4829 | 2.4829 | 3.4829 | −0.2096 | +0.3497 | +0.0153 | −0.1604 | −0.3368 | 2.6433 |
| 7 | H | $CH_3$ | H | Inactive | Inactive | 0.1549 | – | −0.2086 | +0.3492 | +0.0162 | −0.1659 | −0.3448 | 5.2840 |
| 8 | H | $N(CH_3)_2$ | H | Inactive | Inactive | 0.8224 | 1.4456 | −0.2077 | +0.3487 | +0.0162 | −0.1645 | −0.3462 | 5.0451 |
| 9 | H | $SCH_3$ | H | 0.2073 | 1.1493 | 1.1493 | 2.1493 | −0.2093 | +0.3493 | +0.0159 | −0.1640 | −0.3413 | 4.7849 |
| 10 | H | $SC_2H_5$ | H | – | Inactive | 0.2702 | – | −0.2093 | +0.3492 | +0.0159 | −0.1643 | −0.3416 | 4.9491 |
| 11 | H | $SOCH_3$ | H | 0.2313 | Inactive | 1.0764 | 1.8722 | −0.2096 | +0.3500 | +0.0158 | −0.1642 | −0.3385 | 3.4521 |
| 12 | H | $SO_2CH_3$ | H | Inactive | Inactive | 0.2811 | – | −0.2089 | +0.3508 | +0.0158 | −0.1935 | −0.3443 | 6.0659 |
| 13 | $CH_3$ | Cl | H | 0.9769 | 1.4540 | 2.3079 | 3.1530 | −0.1733 | +0.3452 | +0.0124 | −0.1612 | −0.3382 | 2.8537 |
| 14 | $CH_3$ | $NO_2$ | H | 1.4698 | 2.0719 | 2.6917 | 3.4698 | −0.1713 | +0.3465 | +0.0120 | −0.1588 | −0.3348 | 1.8068 |
| 15 | $CH_3$ | CN | H | 1.1382 | 1.7404 | 2.4393 | 2.7404 | −0.1736 | +0.3452 | +0.0126 | −0.1621 | −0.3393 | 2.2174 |
| 16 | $CH_3$ | $SCH_3$ | H | 0.7724 | 0.8693 | 0.5963 | 2.4714 | −0.1739 | +0.3451 | +0.0128 | −0.1639 | −0.3409 | 4.7018 |
| 17 | $CH_3$ | $N(CH_3)_2$ | H | 0.2908 | 0.8648 | 1.6887 | 2.4669 | −0.1732 | +0.3443 | +0.0131 | −0.1633 | −0.3449 | 4.9612 |
| 18 | $CH_3$ | Cl | F | 1.4807 | 1.7817 | 2.8766 | 3.7817 | −0.1730 | +0.3452 | +0.0131 | −0.1651 | −0.3382 | 2.0922 |
| 19 | $CH_3$ | Cl | Cl | 0.9016 | 1.5037 | 2.8804 | 3.5037 | −0.1725 | +0.3457 | +0.0126 | −0.1574 | −0.3372 | 1.8904 |
| 20 | $CH_3$ | $NO_2$ | F | 2.4955 | 2.5925 | 2.4164 | 4.1945 | −0.1710 | +0.3463 | +0.0126 | −0.1627 | −0.3349 | 0.8730 |
| 21 | $CH_3$ | $NO_2$ | Cl | 1.0407 | 2.1198 | 3.4386 | 3.8188 | −0.1704 | +0.3469 | +0.0122 | −0.1551 | −0.3339 | 1.2987 |
| 22 | $CH_3$ | $NO_2$ | CF | 0.8609 | 1.8609 | 2.7148 | 3.5599 | −0.1732 | +0.3468 | +0.0145 | −0.1623 | −0.3353 | 2.1753 |
| 23 | $CH_3$ | H | F | 0.1271 | 0.8261 | 1.5250 | 2.4281 | −0.1727 | +0.3454 | +0.0138 | −0.1699 | −0.3441 | 4.5398 |
| 24 | $CH_3$ | F | F | 0.1457 | Inactive | 0.3325 | 1.7574 | −0.1710 | +0.3451 | +0.0133 | −0.1645 | −0.3424 | 2.9204 |
| 25 | $CH_3$ | $N(CH_3)_2$ | Cl | 0.3391 | 0.6121 | 2.8162 | 1.9131 | −0.1723 | +0.3446 | +0.0133 | −0.1595 | −0.3437 | 4.2738 |

[a] A dash indicates no data available. [b] Inclined screen test measures sedative and muscle relaxant effects in mice. The $ED_{50}$ was the dose which caused three out of six mice to slide off a 70° inclined screen.[8] [c] Fighting mice or footshock test measures taming activity. The MED was that required to tame pairs of fighting mice (three observations), their agression being stimulated by an electrical current applied to their feet. This method is due to Tedeschi et al.[17] [d] Metrazole (pentylenetetrazole) test measures anticonvulsant activity. The $ED_{50}$ was the dose which prevented convlusions in 50% of the mice tested after subcutaneous administration of 125 mg/kg. This method is due to Everett and Richards.[18] [e] Cat. measures sedation and muscle relaxation in cats. The MED was the dose required to produce relaxation of the body and hind legs when the cats were suspended by the scruff of the neck.[19]

Table II. Correlation Coefficients and $t$ Values for Four Tests of Drug Activity Compared with CNDO Data

| CNDO parameters | Correlation coeff IS | FS | Met | Cat. | $t$ values IS[a] | FS[b] | Met[c] | Cat.[a] |
|---|---|---|---|---|---|---|---|---|
| $q_{N_1}$ | 0.2540 | 0.4255 | 0.4538 | 0.3733 | 1.1447 | 1.9386 | 2.4423 | 1.7540 |
| $q_{C_2}$ | 0.0708 | −0.1356 | 0.3187 | −0.1323 | 0.3094 | 0.5643 | 1.6125 | 0.5818 |
| $q_{C_3}$ | −0.4276 | 0.5320 | −0.5509 | 0.4975 | 2.0619 | 2.5905 | 3.1657 | 2.4999 |
| $q_{N_4}$ | 0.3543 | 0.3660 | 0.5752 | 0.4046 | 1.6515 | 1.6216 | 3.3723 | 1.9285 |
| $q_O$ | 0.7517 | 0.8513 | 0.7299 | 0.8255 | 4.9689 | 6.6885 | 4.8927 | 6.3744 |
| $\mu$[d] | 0.7526 | −0.8682 | 0.8240 | −0.8104 | 4.9812 | 7.2131 | 6.6644 | 6.0274 |

[a] 21 data points considered. [b] 19 data points considered. [c] 23 data points considered. [d] Dipole moment in Debyes.

Table III. Drug Activities and CNDO Data for Some Substituted 1,4-Benzodiazepin-2-ones

| No. | Substituents | Drug activities[h] | | | | Carbonyl oxygen charge $q_o$ | Dipole moment $\mu$ (Debye) |
|---|---|---|---|---|---|---|---|
| | | IS[a] | FS[b] | Met[c] | Cat.[d] | | |
| 26 | $R_6$ = Cl | Inactive | Inactive | 0.1311 | - | -0.3391 | 4.6714 |
| 27 | $R_8$ = Cl | Inactive | Inactive | -0.0917 | - | -0.3383 | 3.6176 |
| 28 | $R_9$ = $NO_2$ | -0.2503 | Inactive | Inactive | - | -0.3304 | 7.2758 |
| 29 | $R_8$ = $CF_3$ | -0.1703 | Inactive | - | - | -0.3376 | 3.3982 |
| 30 | $R_7$ = $NO_2$; $R_9$ = $CH_3$ | 1.1688 | 1.1688 | 1.5613 | 2.7709 | -0.3354 | 1.9013 |
| 31 | $R_7$ = Cl; $R_9$ = Cl | 0.3081 | Inactive | 1.5651 | 2.1831 | -0.3330 | 3.4671 |
| 32 | $R_7$ = $CH_3$; $R_9$ = $CH_3$ | -0.2316 | 0.4216 | Inactive | - | -0.3458 | 5.2331 |
| 33 | $R_7$ = $CH_3$; $R_8$ = $CH_3$ | Inactive | Inactive | 0.2978 | - | -0.3453 | 5.4390 |
| 34 | $R_7$ = Br | 1.1002 | 1.1971 | 2.1971 | 2.7992 | -0.3364 | 1.7550 |
| 35 | $R_7$ = Br; $R_8$ = $OCH_3$ | 0.3616 | 0.6346 | 1.6626 | - | -0.3372 | 3.9638 |
| 36 | $R_7$ = Br; $R_2'$ = F | 1.5223 | 2.1244 | 2.8233 | 3.8233 | -0.3365 | 0.3495 |
| 37 | $R_7$ = Cl; $R_2'$ = F | 0.8580 | 1.7611 | 3.4601 | 3.7611 | -0.3382 | 2.3094 |
| 38 | $R_7$ = Cl; $R_3'$ = F | 0.1590 | 0.8580 | 1.8368 | 2.1590 | -0.3374 | 2.1137 |
| 39 | $R_7$ = Cl; $R_4'$ = F | Inactive | Inactive | Inactive | Inactive | -0.3380 | 3.3731 |
| 40 | $R_7$ = Cl; $R_2'$ = Br | 0.8443 | 1.8443 | 2.7651 | 4.0661 | -0.3366 | 2.4446 |
| 41 | $R_7$ = Cl; $R_2'$ = Cl | 0.4842 | 0.8821[e] | 2.8821 | 3.4842 | -0.3371 | 2.1034 |
| 42 | $R_7$ = Cl; $R_2'$ = $OCH_3$ | 0.0007 | 0.4778 | 1.6027 | 2.4778 | -0.3399 | 2.6502 |
| 43 | $R_7$ = Cl; $R_3'$ = $OCH_3$ | Inactive | Inactive | 2.2225 | - | -0.3385 | 2.1658 |
| 44 | $R_7$ = Cl; $R_4'$ = $OCH_3$ | Inactive | Inactive | -0.4253 | - | -0.3395 | 2.0264 |
| 45 | $R_7$ = Cl; $R_2'$ = $CH_3$ | 0.2779 | 0.4540 | 1.5675 | 2.7550 | -0.3393 | 3.1012 |
| 46 | $R_7$ = Cl; $R_3'$ = $CH_3$ | Inactive | Inactive | 0.8519 | - | -0.3391 | 3.1105 |
| 47 | $R_7$ = CN; $R_2'$ = F | 0.5705 | 1.7466 | 2.6327 | 3.7466 | -0.3401 | 1.2461 |
| 48 | $R_7$ = $NO_2$; $R_2'$ = F | 1.8736 | 2.1746 | 2.4934[f] | 3.7767 | -0.3341 | 0.7528 |
| 49 | $R_7$ = $NO_2$; $R_2'$ = Cl | Inactive | 1.1979 | 3.2948 | 3.8000 | -0.3330 | 1.1864 |
| 50 | $R_7$ = $NO_2$; $R_2'$ = $CF_3$ | 0.5428 | 1.5428 | 2.6977 | 3.5424 | -0.3353 | 2.1393 |
| 51 | $R_7$ = $NO_2$; $R_2'$ = $NO_2$ | Inactive | 0.9112 | 2.9691 | - | -0.3363 | 3.8130 |
| 52 | $R_7$ = $NO_2$; $R_3'$ = $NO_2$ | -0.0888 | Inactive | 0.8142 | - | -0.3296 | 4.8149 |
| 53 | $R_7$ = $CF_3$; $R_2'$ = $CF_3$ | 1.0934 | 1.2695 | 1.9685 | 2.8716 | -0.3423 | 2.7846 |
| 54 | $R_7$ = Cl; $R_2'$ = Cl; $R_4'$ = Cl | Inactive | Inactive | -0.3724 | Inactive | -0.3553 | 2.1560 |
| 55[g] | $R_1$ = $CH_3$; $R_7$ = Cl; $R_4'$ = Cl | 0.5037 | Inactive | Inactive | - | -0.3359 | 3.8260 |
| 56 | $R_5$ = pyridyl | 0.0737 | Inactive | -0.2273 | - | -0.3427 | 4.4003 |
| 57 | $R_5$ = pyridyl; $R_7$ = Cl | 0.5586 | 1.4337 | 2.7094 | 2.7347 | -0.3387 | 2.8185 |
| 58 | $R_5$ = pyridyl; $R_7$ = $CF_3$ | 1.4843 | 1.4843 | 2.4843 | 3.4843 | -0.3364 | 2.6877 |
| 59 | $R_5$ = pyridyl; $R_7$ = Br | 1.0224 | 1.4995 | 2.1397 | 3.1985 | -0.3385 | 2.6719 |

[a] Inclined screen test measures sedative and muscle relaxant effects in mice. The $ED_{50}$ was the dose which caused three out of six mice to slide off a 70° inclined screen.[8] [b] Fighting mice or footshock test measures taming activity. The MED was that required to tame pairs of fighting mice (three observations), their agression being stimulated by an electrical current applied to their feet. This method is due to Tedeschi et al.[17] [c] Metrazole (pentylenetetrazole) test measures anticonvulsant activity. The $ED_{50}$ was the dose which prevented convulsions in 50% of the mice tested after subcutaneous administration of 125 mg/kg. This method is due to Everett and Richards.[18] [d] Cat. measures sedation and muscle relaxation in cats. The MED was the dose required to produce relaxation of the body and hind legs when the cats were suspended by the scruff of the neck.[19] [e] This datum is obtained from the more widely quoted value of 40 mg/kg for the $ED_{50}$,[7,10-12] instead of the value of 2 mg/kg quoted in ref 8. [f] This datum is obtained from the more modern value of 0.96 mg/kg for $ED_{50}$, ref 10, p 16, instead of the value of 0.3 mg/kg quoted in ref 8. [g] Data taken from ref 13, p 255. [h] A dash indicates no data available.

If the regressions obtained have a general applicability, then they should predict a required dose in excess of this limiting dose for an inactive compound. For this reason compound **39**, a 4'-fluoro-substituted compound, was included in Table III. Although totally inactive, the regressions predict a required dose below the limiting dose for each test. This failure to explain inactivity has been noted for several other compounds of this series, not included here.[20] It appears that the lack of activity of compound **39** cannot be accounted for either on the basis of the electronic factors considered in the present work or by geometrical features elucidated by x-ray analysis.[14]

In general we note that the dipole moment shows a better correlation with drug activity than does the charge density on the carboxyl oxygen atom. However, if the dipole moment were a causal quantity then there is a problem relating to the fact that its correlation with drug activity is always negative. This might be due to a binding process which involves dipole interactions removing the drug molecules from active service.

It should also be noted that the positive linear correlation with oxygen charge density and the negative correlation with dipole moment are general for the four types of CNS depressant activity considered. Any variation in the ratio of the four activities with change in molecular structure would not be apparent from the relationships with these parameters. This limits the usefulness of the regressions, since it is a general aim to synthesize drugs with low general sedative effect (here measured by the inclined screen test), but with a high specific therapeutic benefit, e.g., antianxiety effect (here measured by the footshock test).

This fact, along with the inability of the regressions to predict the inactivity of compounds and with the marginal significance of some of the regressions, severely limits their use for predictive purposes. However, it is hoped that the observed relationships may aid the development of a mechanistic rationale for the compounds.

## Experimental Section

The CNDO/2 data were obtained by means of a modified version of QCPE 141, run on the CDC 7600 system of the University of London.

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# Potential Long-Acting Anticonvulsants. 2. Synthesis and Activity of Succinimides Containing an Alkylating Group on Nitrogen or at the 3 Position

Milton J. Kornet,* A. Michael Crider,

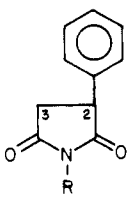
*College of Pharmacy, University of Kentucky, Lexington, Kentucky 40506*

and Edward O. Magarian

*College of Pharmacy, North Dakota State University, Fargo, North Dakota 58102.* *Received January 24, 1977*

The synthesis of succinimide derivatives in which alkylating groups have been attached to the imide nitrogen or to the 3 position of the ring is described. The synthesis of one bis-alkylating derivative **19** is also described. The alkylating groups used were (a) α-haloacetyl, (b) α-haloacetamido, (c) maleamyl, and (d) maleimido. These compounds were prepared as potential long-acting anticonvulsants. None of the compounds showed activity against maximal electroshock or metrazole-induced seizures.

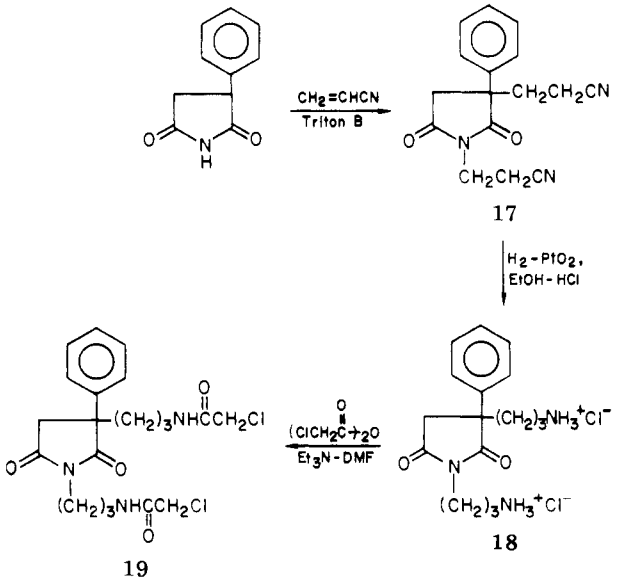
In a previous report[1] we described the synthesis and biological activity of potential long-acting succinimide anticonvulsants. Alkylating groups were attached at the 2 position of the ring and at the para position of the 2-phenyl substituent of phensuximide (**1**, R = $CH_3$). We now report the synthesis and biological activity of compounds in which the alkylating group is attached predominantly to the imide nitrogen. In addition, one compound containing an alkylating group at the 3 position and an *N*,-2-bis-alkylating derivative are described. The alkylating groups used include (a) α-haloacetyl, (b) α-haloacetamido, (c) maleamyl, and (d) maleimido. These groups were attached at varying distances from the imide nitrogen in an effort to search the area at or adjacent to the active site for an appropriate nucleophile. Proper positioning of the alkylating group to a nucleophile species (SH, $NH_2$, $COO^-$, or OH), at or near the active site, can result in a rapid neighboring group reaction with covalent bond formation. Attachment of the succinimide derivative to its active site via covalent bond formation should result in an unusually long-acting anticonvulsant.



1

**Chemistry.** The 2-phenylsuccinimides containing an alkylating group attached to the nitrogen atom and their precursors were obtained for the most part by conventional procedures.[1] Methods for others are described in the Experimental Section. The physical properties of the compounds are given in Table I.

Scheme I




In an attempt to produce an ultra long-acting anticonvulsant, our efforts were turned toward the preparation of the bis-alkylating compound **19**. The synthetic pathway is shown in Scheme I.

Introduction of an alkylating group into the 3 position of the succinimide ring was accomplished by the route shown in Scheme II. The NMR spectrum of **23** showed