# HYDROLYTIC STABILITY AND PESTICIDAL ACTIVITY OF N'-METHYL- AND N'-ARYLCARBAMATES OF 3-(N,N-DIETHYLAMINO)PHENOL

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Twelve carbamates based on 3-(N,N-diethylamino)phenol have been prepared, and their hydrolysis rate in aqueous media of pH 7–12·5, their inhibition of butyrylcholin esterase and acetylcholin esterase and herbicidal activity have been studied. The hydrolysis of the compounds studied in the mentioned media proceeds by the ElcB mechanism, the value of reaction constant at 25°C is $\varrho = 1{\cdot}12 \pm 0{\cdot}08$. The hydrolysis rate in the pH region 7–8·5 is affected by protonation of the 3-N,N-diethylamino group. The compounds *I*–*XII* inhibit butyrylcholin esterase ($pI_{50}$ value 5·1–6·5). Acetylcholin esterase is inhibited most efficiently by the carbamates *XII* ($pI_{50} = 8{\cdot}3$), *XI* ($pI_{50} = 6{\cdot}25$) and *VII* ($pI_{50} = 5{\cdot}07$). Herbicidal effects are small, the effective dose being above 5 kg/ha.

Carbamates have insecticidal, herbicidal and fungicidal effects[1–3]. Compared with organophosphates, the insecticidal carbamates have substantially lower toxicity and stability, and their hydrolysis and metabolism produce little toxic or harmless products[4,5]. Herbicidal carbamates have the same properties[6].

For a detailed investigation of hydrolytic stability of 3-(N,N-diethylamino)phenyl carbamates we synthetized twelve derivatives by reactions of 3-(N,N-diethylamino)-phenol with methyl and aryl isocyanates. These derivatives were hydrolyzed in aqueous medium at pH 7–12·5 and submitted to herbicidal, antibutyrylcholin esterase and antiacetylcholin esterase tests.

## EXPERIMENTAL

### Reagents

3-(N,N-*Diethylamino*)*phenyl* N'-*arylcarbamates* I–X were prepared by reactions of 3-(N,N-diethylamino)phenol with aryl isocyanates. 0·05 mol 3-(N,N-diethylamino)phenol in 30 ml tetrahydrofuran was treated with the solution of 0·06 mol aryl isocyanate in 20 ml tetrahydrofuran added during 1 h. The mixture was refluxed 2 h and left to stand at room temperature 24 h. The precipitated carbamate was filtered off and recrystallized from chloroform–n-pentane mixture. Physical constants of the synthetized derivatives are given in Table I.

3-(N,N-*Diethylamino)phenyl*-N'-*methylcarbamate* (XI). Solution of 16·4 g 3-(N,N-diethylamino)phenol in 20 ml tetrahydrofuran was treated with 10 ml methyl isocyanate added during 1 h. The reaction was catalyzed with 1 ml triethylamine. The mixture was left to stand 24 h, and the separated crystals of the carbamate were collected by suction; m.p. 83—86°C (benzene–n-heptane). Yield 82%. For $C_{12}H_{18}N_2O_2$ (222·3) calculated: 64·84% C, 8·16% H, 12·60% N; found: 64·92% C, 8·14% H, 12·57% N.

3-(N'-*Methylcarbamoyloxy*)-N-*methyl*-N-*diethylanilinium iodide* (XII). 5 g Carbamate *XI* was dissolved in 100 ml benzene and treated with 20 ml methyl iodide. The mixture was refluxed 12 h, and the product was precipitated by addition of 100 ml n-hexane. M.p. 152—153·5°C (chloroform–n-hexane), yield 34%; for $C_{13}H_{21}IN_2O_2$ (364·2) calculated: 42·87% C, 5·81% H, 7·69% N; found: 42·55% C, 5·51% H, 7·83% N.

TABLE I

3-(N,N-Diethylamino)phenyl N'-arylcarbamates

| Compound | M.p., °C (Yield, %) | Formula (Mol.mass) | Calculated/Found | | |
|---|---|---|---|---|---|
| | | | % C | % H | % N |
| *I* | 167—170 (75) | $C_{17}H_{19}N_3O_4$ (329·4) | 61·99 61·90 | 5·81 5·67 | 12·76 12·63 |
| *II* | 114—116 (83) | $C_{17}H_{19}N_3O_4$ (329·4) | 61·99 62·38 | 5·81 5·73 | 12·76 12·59 |
| *III* | 75—80 (88) | $C_{18}H_{19}F_3N_2O_2$ (352·4) | 61·36 61·17 | 5·44 4·87 | 7·95 8·04 |
| *IV* | 154—157 (72) | $C_{19}H_{22}N_2O_3$ (342·4) | 69·92 70·38 | 6·79 6·71 | 8·52 8·24 |
| *V* | 78—80 (90) | $C_{17}H_{19}ClN_2O_2$ (318·8) | 64·05 63·74 | 6·00 6·01 | 8·79 8·66 |
| *VI* | 154—155 (92) | $C_{17}H_{19}ClN_2O_2$ (318·8) | 64·05 63·89 | 6·00 5·86 | 8·79 8·74 |
| *VII* | 96—98 (92) | $C_{17}H_{20}N_2O_2$ (284·4) | 71·80 71·60 | 7·09 7·22 | 9·85 9·97 |
| *VIII* | 77—80 (85) | $C_{18}H_{22}N_2O_2$ (298·4) | 72·45 72·66 | 7·43 7·58 | 9·39 9·10 |
| *IX* | 112—114 (88) | $C_{18}H_{22}N_2O_2$ (298·4) | 72·45 72·22 | 7·43 7·70 | 9·39 9·17 |
| *X* | 136—137 (78) | $C_{18}H_{22}N_2O_3$ (314·4) | 68·77 68·85 | 7·05 7·19 | 8·91 8·48 |

Kinetic Measurements

Concentration decrease of the starting compound was followed in the pH region 8–12 continuously at 265 nm. 2·95 ml buffer solution was placed in 1 cm quartz cell (Zeiss PMQ II spectrophotometer), and after 10 min temperation 0·05 ml solution of $2{\cdot}4 \cdot 10^{-3}$ mol $l^{-1}$ carbamate in dioxane was added. In the pH region 7–8 the hydrolysis was carried out discontinuously: 98 ml buffer solution was placed in a flask in thermostat, and after 15 min 2 ml solution of $2 \cdot 10^{-3}$ mol $\cdot l^{-1}$ carbamate in dioxane was added. At definite time intervals samples were withdrawn, cooled at 25°C and their absorbance measured with the Zeiss PMQ II spectrophotometer at 265 nm.

The rate constants were calculated from the relation $k \cdot t = 2{\cdot}303 \log (E_0 - E_\infty)/(E_t - E_\infty)$, where $k$ is the rate constant in $s^{-1}$, $E_0$ is extinction at the time $t = 0$, $E_t$ is the extinction at a time $t$, and $E_\infty$ is the extinction after 9 reaction half-lives. The hydrolysis rate constants measured at 40–70°C were recalculated for the temperature 25°C with the use of the relation $\log k = \log A - E/(19{\cdot}146T)$, the activation energies being given in Table II. The obtained logarithms of the hydrolysis rate constants at 25°C are given in Table III for the carbamates *I*–*X*.

Biochemical Measurements

*Inhibition of butyrylcholine esterase* (from horse blood serum, activity 4U/mg, Merck, Darmstadt) was measured according to Ellman[7]. Five test tubes were charged with 0·2–2 ml $5 \cdot 10^{-3}$ mol $l^{-1}$ solution of carbamates *I*–*XII*, the sixth test tube was charged with 1 ml $5 \cdot 10^{-2}$ mol $l^{-1}$ solution of the same carbamate, and volume in each test tube was adjusted at 3 ml by addition of phosphate buffer (100 92 g $Na_2HPO_4.2\,H_2O$ + 3·24 g $KH_2PO_4$ in 3 l aqueous solution). Into each test tube 3 ml solution of butyrylcholin esterase in the abovementioned phosphate buffer (activity 0·25 U/ml) was added, the test tubes were shaken and allowed to stand 5 min. Thereafter 3 ml indication solution (0·1 g acetylthiocholin iodide and 0·125 g 5,5′-dithiobis(2-nitrobenzoic acid) in 500 ml of the abovementioned buffer) was added, and extinction was measured at 412 nm after 10 min. The resulting carbamate concentrations in the individual test tubes were: $1{\cdot}11 \cdot 10^{-4}$ mol $l^{-1}$, $2{\cdot}77 \cdot 10^{-4}$ mol $l^{-1}$, $5{\cdot}55 \cdot 10^{-4}$ mol $l^{-1}$, $1{\cdot}66 \cdot 10^{-3}$ mol $l^{-1}$, $2{\cdot}22 \cdot 10^{-3}$ mol $l^{-1}$, and $5{\cdot}55 \cdot 10^{-3}$ mol $l^{-1}$. From the found values the percentage of the blocked butyrylcholin esterase was calculated, and with the use of the probit-concentration diagram the

TABLE II

Activation energies of hydrolysis of compounds *I*–*X* at pH 6·9–9·7

| Compound | $E$, kJ mol$^{-1}$ | Compound | $E$, kJ mol$^{-1}$ |
|---|---|---|---|
| *I* | 90·2 ± 3·8 | *VI* | 102·7 ± 3·5 |
| *II* | 93·8 ± 2·6 | *VII* | 108·0 ± 3·4 |
| *III* | 95·6 ± 3·1 | *VIII* | 106·3 ± 3·8 |
| *IV* | 99·4 ± 1·8 | *IX* | 112·6 ± 4·4 |
| *V* | 98·2 ± 4·6 | *X* | 115·5 ± 4·9 |

TABLE III

The values log $k$ of hydrolysis of compounds *I*—*X* at 25°C

| pH | *I* | *II* | *III* | *IV* | *V* |
|---|---|---|---|---|---|
| 6·90 | −4·150[a] | −4·280[a] | — | — | — |
| 7·20 | −4·110[a] | −4·150[a] | — | — | — |
| 7·95 | −3·880[a] | −4·030[a] | −4·250[a] | −4·382[a] | −4·390[a] |
| 8·40 | −3·640[a] | −3·871[a] | −4·080[a] | −4·200[a] | −4·260[a] |
| 9·70 | −2·653 | −2·847 | −3·213 | −3·368 | −3·377 |
| 10·60 | −1·948 | −1·922 | −2·372 | −2·435 | −2·520 |
| 11·25 | −1·302 | −1·401 | −1·725 | −1·894 | −1·839 |
| 11·75 | −1·000 | −1·050 | −1·177 | −1·390 | −1·560 |
| 12·10 | — | — | −1·040 | −1·249 | −1·300 |

| pH | *VI* | *VII* | *VIII* | *IX* | *X* |
|---|---|---|---|---|---|
| 7·95 | −4·420[a] | −4·521[a] | −4·584[a] | — | — |
| 8·40 | −4·310[a] | −4·452[a] | −4·487[a] | −4·503[a] | −4·560[a] |
| 9·70 | −3·396 | −3·714[a] | −3·756[a] | −3·760[a] | −3·873[a] |
| 10·60 | −2·601 | −2·615 | −2·935 | −2·945 | −2·977 |
| 11·25 | −2·080 | −2·202 | −2·358 | −2·394 | −2·457 |
| 11·75 | −1·671 | −1·820 | −1·950 | −1·971 | −1·988 |
| 12·10 | −1·410 | −1·533 | −1·720 | −1·715 | −1·763 |

[a] The extrapolated value log $k$.

TABLE IV

Inhibition of acetyl- (ACE) and butyrylcholin esterase (BCE) by the carbamates *I*—*XII*

| Compound | $pI_{50}$ | | Compound | $pI_{50}$ | |
|---|---|---|---|---|---|
| | ACE | BCE | | ACE | BCE |
| *I* | — | 5·02 | *VII* | 5·07 | 5·40 |
| *II* | — | 5·75 | *VIII* | — | 5·40 |
| *III* | — | 5·11 | *IX* | — | 5·66 |
| *IV* | — | 5·20 | *X* | 3·20 | 6·26 |
| *V* | — | 5·72 | *XI* | 6·26 | 5·96 |
| *VI* | 2·80 | 6·45 | *XII* | 8·70 | 4·55 |

values $I_{50}$ were obtained whose negative logarithms ($pI_{50}$) are given in Table IV. Inhibition of acetylcholin esterase was measured by the procedure given in ref.[8], and the obtained $pI_{50}$ values are given in Table IV, too.

*Herbicidal tests* were carried out at concentrations 5 kg/ha both in pre-emergent and post-emergent application in the following way: clayey-sandy soil was placed in vessels with surface area 0·04 $m^2$, the layer thickness 5·5 cm, and the indicator plants were sowed therein and watered. The tested carbamates were applied in water emulsions in concentrations corresponding to 5 kg/ha. Condition of the plants was evaluated after three days and then after three weeks, the second evaluation being decisive. Degrees of the effects: 0 healthy plants, 1 little attacked plants, 2 perceptibly attacked plants, 3 strongly attacked plants, 4 heavily damaged plants, 5 dead or non-germinated plants. The post-emergent application was carried out with grown plants by spraying with aqueous emulsion of the tested substance of 0·5 and 0·1% concentration. The plants were watered in such way, that the substances might not be washed down from the leaves. The tests were evaluated as above. The results are given in Table V.

## RESULTS AND DISCUSSION

From Fig. 1 and Table III it follows that the hydrolysis of 3-(N,N-diethylamino)-phenyl N'-arylcarbamates proceeds by the ElcB mechanism in the pH region 7 to 12·5, which is supported also by value of slope of the dependence log $k$ *vs* pH (equal to 1·1) and value of the reaction constant $\varrho = 1{\cdot}12 \pm 0{\cdot}08$ which stand in accordance with the earlier published results[9]. The change in straight line character of pH profiles of the carbamates $I-X$ in the pH region 7–9 is ascribed to protonation of 3-N,N-diethylamino group, as already mentioned in ref.[10]. On the basis of the found hydrolysis rate constants the studied carbamates can be denoted as relatively

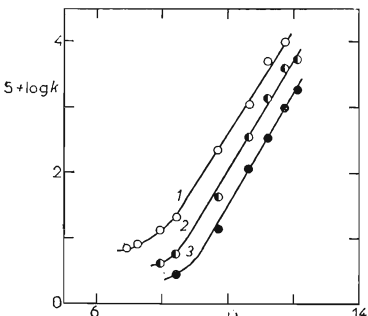



FIG. 1

pH Dependence of log $k$ of hydrolysis of carbamate $I$ (curve 1), $V$ (curve 2), and $X$ (curve 3) at 25°C

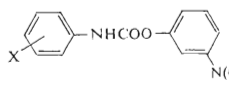
stable, their decomposition half-life in aqueous medium of pH 7 being about 5 days. The stability increases in acidic medium, in alkaline medium it is decreased approximately 10 times per one pH unit.

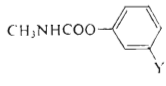
On the basis of the results of biochemical tests given in Table IV the studied compounds can be denoted as good inhibitors of butyrylcholin esterase. Some of the derivatives also inhibited the acetylcholine esterase obtained from rat brain, a very high inhibition of acetylcholin esterase being found with 3-(N'-methylcarbamoyloxy)--N-methyl-N,N-diethylanilinium iodide (*XII*) with $pI_{50} = 8{\cdot}7$, $I_{50} = 1{\cdot}6 \cdot 10^{-9}$ mol . $l^{-1}$. On the contrary, the same carbamate *XII* inhibited butyrylcholin esterase at substantially higher concentration, $pI_{50} = 4{\cdot}55$, $I_{50} = 2{\cdot}8 \cdot 10^{-5}$ mol $l^{-1}$, hence the substance is a strong and specific acetylcholin esterase inhibitor, acting as a very strong poison in intravenous application ($LD_{50} = 1{\cdot}22$ mg/kg for rats). However, this carbamate cannot be used as contact insecticide due to its low lipophilic solubility which lowers its penetration through insect cuticle very much. The second, according to activity, is the carbamate *XI* which inhibits acetylcholin esterase in the same concentration as the commercially produced insecticide Sevin (its active substance is 1-naphthyl N-methylcarbamate). Out of the series of the arylcarbamates *I*–*X*, inhibition properties for acetylcholin esterase were only found with the derivatives *VI*, *VII*, and *X*, only the carbamate *VII* being active at lower concentration (see Table IV). The decreasing inhibition properties for acetylcholin esterase were

TABLE V

Herbicidal activity of the carbamates *I*–*X* for 5 kg/ha dose

| Plant | *I* | *II* | *III* | *IV* | *V* | *VI* | *VII* | *VIII* | *IX* | *X* | S[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Pre-emergent | | | | | |
| *Avena sativa* | 0 | 0 | 1 | 0 | 2 | 2 | 1 | 2 | 1 | 1 | 5 |
| *Fagopyrum vulgare* | 0 | 0 | 1 | 1 | 3 | 3 | 2 | 2 | 1 | 2 | 5 |
| *Sinapis alba* | 1 | 1 | 3 | 2 | 4 | 4 | 4 | 3 | 2 | 2 | 5 |
| *Panicum miliaceum* | 0 | 0 | 1 | 0 | 2 | 1 | 0 | 0 | 0 | 0 | 5 |
| *Lepidium sativum* | 0 | 0 | 2 | 1 | 3 | 3 | 1 | 1 | 1 | 1 | 5 |
| | | | | | | Post-emergent | | | | | |
| *Avena sativa* | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 5 |
| *Fagopyrum vulgare* | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 5 |
| *Sinapis alba* | 0 | 0 | 1 | 0 | 2 | 2 | 0 | 0 | 1 | 1 | 5 |
| *Panicum miliaceum* | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 |
| *Lepidium sativum* | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 5 |





*I*, X = 4-$NO_2$
*II*, X = 3-$NO_2$
*III*, X = 3-$CF_3$
*IV*, X = 4-$COCH_3$
*V*, X = 3-Cl
*VI*, X = 4-Cl
*VII*, X = H
*VIII*, X = 3-$CH_3$
*IX*, X = 4-$CH_3$
*X*, X = 4-$OCH_3$

*XI*, Y = $N(C_2H_5)_2$
*XII*, Y = $\overset{(+)}{N}(C_2H_5)_3\ I^{(-)}$

also accompanied by strong decrease in toxicity of the said carbamates. The carbamate *XI* has $LD_{50}$ = 91 mg/kg, the carbamate *VII* is practically non-toxic, its $LD_{50}$ being above 10 g/kg (for rats Vistar). Results of the herbicidal tests are given in Table V wherefrom it can be seen that the investigated group of carbamates does not possess sufficient herbicidal effects. Also no specific herbicidal activity was found.

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