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Carbamates: Are they "Good" or "Bad Guys"?

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In this short review, we address carbamates, a class of chemical compounds derived from carbamic acid, which have garnered attention as both valuable assets and potential hazards across diverse applications. Their stable structure, characterized by the R–O–CONH–R functional group, allows for various substituents, enabling their use in medicine, agriculture, and even as chemical warfare agents. In medicine, carbamates play a significant role as components of numerous medications approved by Food and Drug Administration. The stability and permeability properties of carbamates have led to the enhancement of various pharmacological compounds, aiding drug development. In agriculture, carbamates have been used as pesticides to manage pests and increase crop productivity. Despite their effectiveness, overuse and inadequate regulation have raised concerns about environmental contamination and health risks. In this review, we also seize the opportunity to present information to the readers about the framework of international agreements on toxic compounds, highlighting their potential misuse as chemical warfare agents and how they have been a reason of concern, with their high toxicity across various exposure pathways. The inclusion of certain carbamates in the Chemical Weapons Convention underscores their lethal nature. However, they lack comprehensive research, raising questions about their complete effects and potential countermeasures.

Keywords: carbamate, medicine, pesticide, nerve agents, CWC, OPCW

1. General Remarks

Carbamates represent a stable category of chemical compounds derived from carbamic acid, characterized by the presence of the R–O–CO–NH–R bond. These compounds are derived from the less stable carbamic acid (H_2N–COOH) by replacing the amino and carboxyl components with various alkyl or aryl substituents,[1] also found in cyclic scaffolds. In cases where the carbamate group is attached to an inorganic atom, whether metallic or non-metallic, these substances are termed inorganic carbamates.[2] Esters originating from basic carbamic acids usually exhibit instability, especially under alkaline conditions. The ester variations of carbamates exist as crystals characterized by low vapor pressure and modest yet variable water solubility. Their solubility in nonpolar organic solvents like chloroform and toluene is limited, while they exhibit notable solubility in acetone, which is a polar organic solvent.[3]

Their extensive utilization spans across various fields. They find applications in medicine, due to their crucial role in numerous drugs and prodrugs that have been approved by regulatory authorities such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), such as in the treatment of diseases such as Alzheimer's disease, glaucoma and myasthenia gravis.[4] In addition, they serve commercial and agricultural purposes, holding substantial significance in the manufacturing of diverse categories of pesticides, including insecticides, fungicides and herbicides. Furthermore, carbamates function as protective groups for amines, intermediates in organic synthesis, or linkers in combinatorial chemistry. They are also utilized as key components in the production of paints and polyurethanes.[2]

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One significant issue revolves around the uncontrolled utilization of these chemicals in crops. The surge in demand for enhanced agricultural yield has led to the widespread deployment of pesticides for pest control, thereby exacerbating the risks to human welfare.[5] Numerous carbamates were found to be carcinogenic, leading to their banning in the United States and European countries for many years. This ban is not only due to the damage caused to human health, but also stems from adverse impacts on soil, water, air and biodiversity.[6]

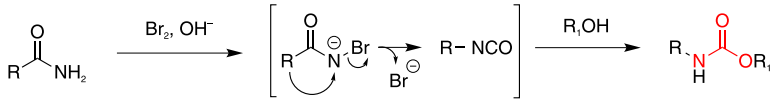
Another concerning aspect related to carbamates is their capability to induce pathophysiological effects that disrupt or impede the normal transmission of neuromuscular impulses, even at low doses. Acetylcholinesterase (AChE) has a critical function in facilitating synaptic transmission in both cholinergic synapses between neurons and neuromuscular junctions.[7] These functions are crucial for various essential biological processes, including heartbeat, respiration, digestion, and brain activity. Despite the well-established significance within nervous systems, there is emerging evidence suggesting that AChE may also exert influences on neural system development, although the precise nature of these effects remains incompletely elucidated.[8] Similar to organophosphate nerve agents, carbamates act as AChE inhibitors. A fundamental differentiation between carbamates and organophosphates lies in their acetylcholinesterase binding mechanism. Carbamates form a reversible bond with acetylcholinesterase, whereas organophosphates lead to irreversible phosphorylation of the enzyme. The coupling of the enzyme-inhibitor complex before carbamoylation is crucial for effective anticholinesterase activity.[9] Consequently, since the 1940s, they have been under investigation as plausible chemical warfare agents. Certain variants of carbamates have exhibited notable toxicity, occasionally comparable to organophosphate nerve agents like VX.[10] During the 1970s and 80s, multiple patents were issued for carbamate chemical agents featuring both mono and bisquaternary ammonium functional groups, underscoring their potential as novel nerve agents for warfare and utilization in ammunitions.[11] Due to this history of research and development, in 2019, two representative families of carbamates were added to Schedule 1A of the Chemicals Annex of the Chemical Weapons Convention (CWC).[12]

To gain deeper insights into the significance of carbamates and to determine their potential benefits or drawbacks, as "good" or "bad" guys, we conducted a comprehensive literature review including information on carbamates, such as those used in medicine, agriculture and those just included in Schedule 1A of the Annex on Chemicals,[12] as well as on other similar carbamates.

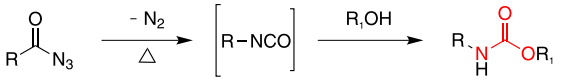
2. Carbamate Synthesis Methods

Due to its relevance in the organic synthesis of carbamates, particularly as a subunit of biologically active compounds, the search for effective and simple approaches in their synthesis has aroused great interest among researchers. Several methods have been developed for the synthesis of carbamates.[2] Among the traditional methods, two can be mentioned that use the rearrangement process, such as Hofmann (Scheme 1) and Curtius (Scheme 2). The first stands out for its ability to convert primary carboxamides into amines or carbamates, through the reduction of a carbon in the molecular structure.[13] Typically, the Hofmann rearrangement uses aqueous NaOH and Br_2 to transform primary carboxamides into amines.[14] Over the past few years, this method has been used in the synthesis of carbamates, involving the formation of an isocyanate intermediate, a crucial component for the polyurethane industries. These isocyanates can then undergo a reaction with alcohols to produce the respective carbamates.[15] The second method, the Curtius rearrangement, uses acylazides to also generate isocyanates through thermal decomposition.[16] This method also finds wide application in the conversion of carboxylic acids to carbamates and ureas.

Another general method for the preparation of carbamate involves the employment of phosgene (Scheme 3) or its derivatives, due to the ability to attach two nucleophilic units to the same carbon atom. This two-component system is especially suitable for the combinatorial synthesis of carbonates, ureas and carbamates.[17] However, phosgene is extremely toxic and a chemical listed in the Schedule 3 of the CWC Annex on Chemicals,[10] which restricts its application. Given this, significant efforts have been directed towards finding an alternative to the phosgene process. Within the possibilities, the use of carbon dioxide (Scheme 4) is considered an attractive option, as it is a classic and environmentally benign (non-toxic, non-corrosive and non-flammable) renewable resource. It is established that the interaction between carbon dioxide

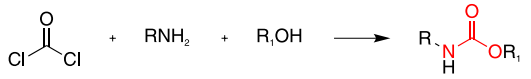


Scheme 1. Carbamate synthesis by Hofmann rearrangement.

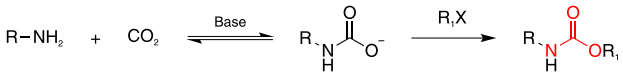


Scheme 2. Carbamate synthesis by Curtius rearrangement.

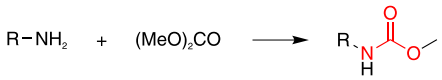
and amines takes place rapidly, leading to the generation of ammonium salts of carbamic acid.[18] Predominantly, approaches in this scenario focus on generating the carbamate anion through the reaction of carbon dioxide with amines, followed by its interaction with electrophiles. However, due to the lower nucleophilicity of the carbamate anion compared to the amine formed at the salt-forming equilibrium, the ensuing reaction of carbamate salts with alkyl halides fails to selectively produce urethanes.[19] In recent years, diverse forms of carbon dioxide have been employed with a range of reagents and catalytic systems, encompassing gaseous, electrochemical, and supercritical.[2] Use of dimethyl carbonate (Scheme 5) as a source of carbamoyl moiety has also been explored in the synthesis of carbamates, due to its non-toxic and more environmental-friendly nature.[20-25]



Scheme 3. Carbamate synthesis by using phosgene.

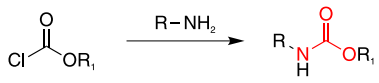


Scheme 4. Synthesis of carbamates using carbon dioxide.



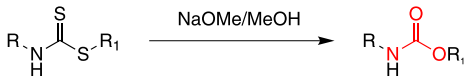
Scheme 5. Synthesis of carbamates using dimethyl carbonate.

Alkyl chloroformates are commonly used reagents known for their reactivity in aminolysis reactions with amines or substituted amines, resulting in the formation of carbamates (Scheme 6). Nevertheless, in order to achieve satisfactory yields, processes are usually time-consuming and requires significant excess of base. Furthermore, they may be impractical for synthesis of elaborated scaffolds, especially in cases where chemoselectivity is required.[26]

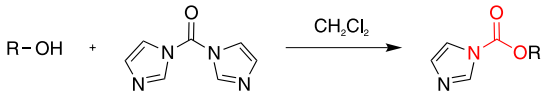


Scheme 6. Synthesis of carbamates using alkyl chloroformate.

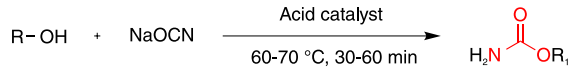
Alternative methods for carbamate synthesis include unconventional approaches, such as the direct conversion utilizing dithiocarbamates with NaOMe/MeOH (Scheme 7);[27] the reaction between 1,1'-carbonyldiimidazole and diverse alcohols under extremely gentle conditions (Scheme 8);[28] the utilization of sodium cyanate to form primary carbamates via the reaction with alcohols, employing a variety of acidic catalysts (Scheme 9);[29] the formation of α-carbamates by reacting different carbonyl compounds with *N*-methyl-*O*-carbamoyl-hydroxylamine hydrochlorides (Scheme 10);[30] and the achievement of diverse substituted aromatic carbamates by reacting a range of aromatic oximes with alcohols, employing methyltrioxorhenium (MTO) and urea-hydrogen peroxide (UHP) (Scheme 11).[31]



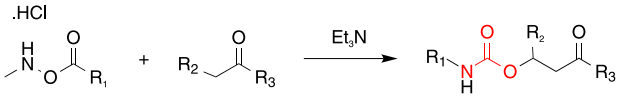
Scheme 7. Synthesis of carbamates using dithiocarbamate.



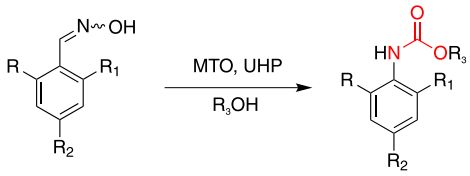
Scheme 8. Synthesis of carbamates using 1,1'-carbonyldiimidazole.



Scheme 9. Synthesis of carbamates using sodium cyanate.



Scheme 10. Synthesis of carbamates using *N*-methyl-*O*-carbamoyl-hydroxylamine hydrochlorides.



Scheme 11. Synthesis of carbamates using oximes.

3. Use in Medicine

In the 19th century, European missionaries in West Africa were the first to document the biological effects of a carbamate. During that time, an indigenous community in the region utilized a white extract derived from Calabar beans (*Physostigma venenosum*) as a substance for ordeal poison during witchcraft trials. Eventually, these beans were brought to Great Britain in the year 1840. In the subsequent year of 1864, researchers Jobst and Hesse successfully isolated a potent alkaloid from the beans, which they named physostigmine. Originally derived from nature, physostigmine is a methylcarbamate ester that found its initial medical use for glaucoma treatment.[32] However, its applications have significantly expanded

over time. Specially, it displays the capacity to greatly enhance muscular strength in individuals dealing with myasthenia gravis. Beyond this, it serves as a treatment for conditions like delayed gastric emptying and instances of anticholinergic intoxication resulting from an excessive consumption of scopolamine, atropine, and similar anticholinergic medications.[32]

Carbamates exhibit desirable chemical attributes, including stability in both conformation and metabolism, coupled with the capability to traverse cell membranes. Notably, certain carbamates can even breach the blood-brain barrier (BBB), a significant feat, indicating that they may exert therapeutic activity in the Central Nervous System (CNS). Scientific investigation has demonstrated that introducing a carbamate moiety augments the biological efficacy of various natural or synthetic compounds featuring active pharmacophores.[7] Through the manipulation of substituents at the amino and carboxyl terminus of the carbamate group, the potential emerges to tailor its biological and pharmacokinetic characteristics, resulting in heightened stability.[33] These qualities have rendered the carbamate group an appealing constituent within the framework of numerous pharmacologically consequential compounds. As a result, significant attention has been aroused in recent times regarding the creation of effective and secure approaches for synthesizing carbamate esters. Illustratively, betulinic acid, a highly promising anticancer medication, witnessed enhancements in both potency and reduced cytotoxicity through the introduction of imidazole and triazole carbamate derivatives, resulting in 12-fold greater efficacy.[4] Similarly, substituting the unsaturated ester chain at position C-6 in fumagillin (known as a natural antibiotic and an inhibitor of endothelial cell proliferation) with the *O*-(chloroacetyl) carbamoyl fragment yielded an antitumor compound exhibiting a potency increased by a factor of 50.[33]

The substantial growth of carbamate utilization within the pharmaceutical domain is additionally propelled by the perception of the carbamate group as a structural counterpart to the amide bond. Recently, certain limitations associated with amide-based compounds have been tackled by adopting carbamates as amido- or peptidomimetics. This strategy has demonstrated its efficacy in elevating drug potency, extending the period of activity, and enhancing precision in target engagement.[34]

Diverse compounds featuring a carbamate entity are presently progressing through various phases of preclinical and clinical trials. Notably, cenobamate (**1**) stands as an illustrative carbamate compound that has recently secured FDA approval.[35] Its specific designation lies in the treatment of partial seizures in the adult population.[35] Currently, numerous FDA approved drugs encompass the carbamate group. This variety includes various categories: cholinesterase inhibitors used to address neurodegenerative disorders (neostigmine (**2**), rivastigmine (**3**), physostigmine (**4**), and pyridostigmine (**5**)), chemotherapeutic agents like irinotecan (**6**) and mitomycin C (**7**), human immunodeficiency virus (HIV) protease inhibitors such as efavirenz (**8**) and ritonavir (**9**), anthelmintics like albendazole (**10**) and mebendazole (**11**), anticonvulsants including retigabine (**12**) and felbamate (**13**), and even muscle relaxants such as metaxalone (**14**) and methocarbamol (**15**)[7] (Figure 1).

An intriguing application of carbamate lies in the preventive, prophylactic treatment for combatants, which involves the daily administration of monoquaternary carbamate pyridostigmine bromide. This approach is recommended as a prophylaxis towards nerve agent intoxication, primarily owing to its capacity for its enzymatic adduct with hydroxyl group of the serine residue of AChE active site undergoes hydrolysis, leading to the enzyme spontaneous reactivation.[36] While its use leads to shorter periods of intoxication in comparison to other organophosphates, careful consideration must be given to potential challenges in medical management, particularly those associated with gastrointestinal issues. These difficulties have once been linked to the phenomenon known as Gulf War sickness. Undoubtedly, the prophylactic use of pyridostigmine carbamate bromide carries several limitations. Its dosage is constrained due to the potential for adverse effects and its inability to traverse the BBB. As a result, pyridostigmine bromide can solely offer protection to peripheral AChE, guarding against irreversible inhibition caused by nerve agents.[37]

4. Carbamate Pesticides

In accordance with the World Health Organization (WHO),[38] "pesticides are chemical compounds that are used to kill pests, including insects, rodents, fungi and unwanted plants (weeds)". Thus, they play a crucial role in both the realms of public health and agriculture, managing disease vectors and crop-damaging pests.

The earliest documented instances of utilizing pesticides trace their origins to ancient times. During this period, various inorganic compounds such as arsenic, antimony, arsenate, barium, boric acid, cadmium, lead, mercury, and thallium were recognized for their application against diverse insects in crops.[39] By the end of the 19th century, the first-generation insecticides entered into the commercial market. These insecticides were formulated using inorganic compounds such as mercuric chloride,

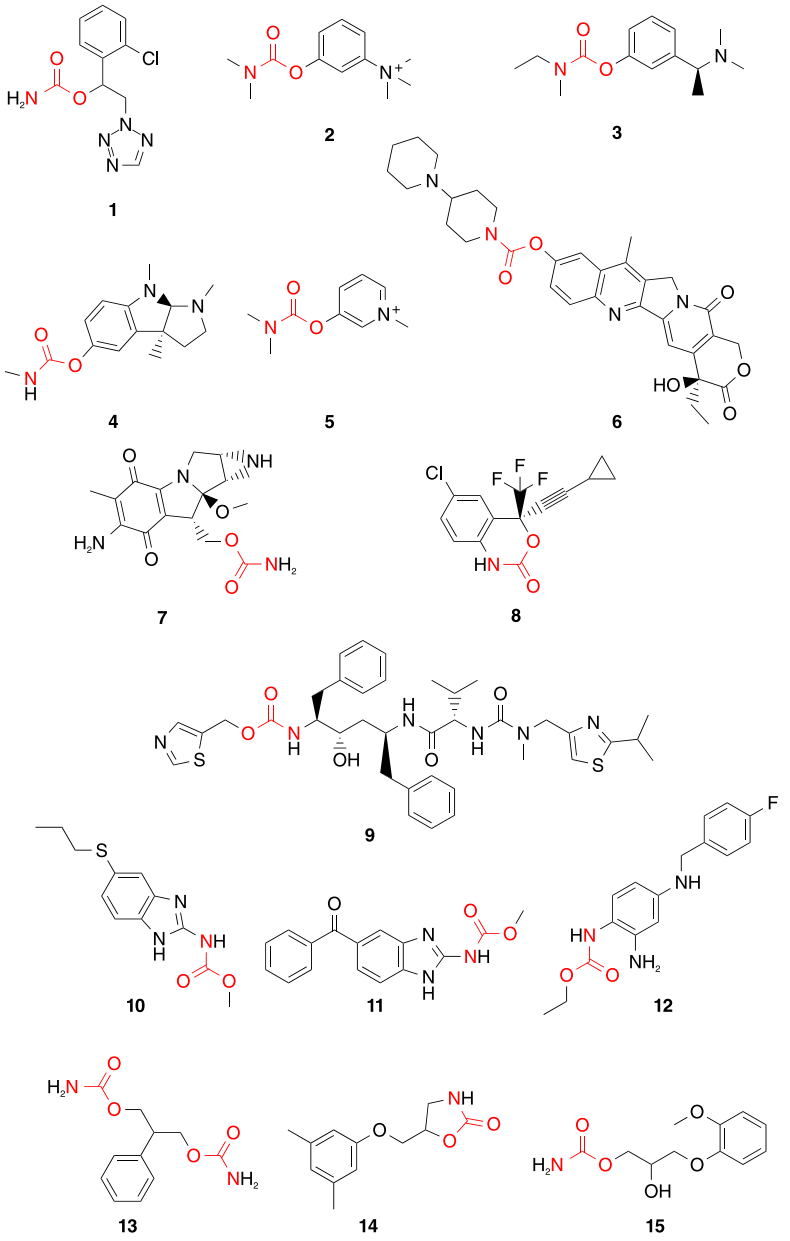


Figure 1. Some carbamates with clinical use: cenobamate (**1**), neostigmine (**2**), rivastigmine (**3**), physostigmine (**4**), pyridostigmine (**5**), irinotecan (**6**), mitomycin C (**7**), efavirenz (**8**), ritonavir (**9**), albendazole (**10**), mebendazole (**11**), retigabine (**12**), felbamate (**13**), metaxalone (**14**) and methocarbamol (**15**).

arsenates derived from aluminum, calcium, lead, or sodium, as well as compounds like metallic arsenites (copper, barium, sodium or selenium).[39] The second generation of insecticides predominantly emerged during World War II, as scientists sought chemicals capable of managing prevalent infestations of that era, including lice and malaria-carrying vectors. During the 1940s, dichlorodiphenyltrichloroethane (DDT, **16**, Figure 2) gained distinction as the primary extensively employed insecticide, finding application not only in agricultural fields but also in households, to manage insect populations, including those acting as carriers of diseases in humans. Nonetheless, owing to their elevated toxicity and the emergence of resistant mosquitoes, the utilization of insecticides based on organochlorine compounds was curtailed and ultimately prohibited in numerous countries spanning the period from the 1940s to the 1960s.[6] Consequently, as a substitute for organochlorine insecticides and to formulate novel approaches for managing insect pests and other plant pathogens, formulations utilizing organophosphates were created. These insecticides, working through the phosphorylation of acetylcholinesterase, offer extensive coverage and diverse levels of toxicity, making them applicable in both agricultural and sanitation contexts. They stand out for their tendency not to accumulate in tissues and for their biodegradability; nonetheless, their

chemical stability remains a concern.[40] Only in the 1950s, that pesticides derived from carbamic acid made their debut in the market.[39] Examples of some carbamate pesticides are carbaryl (**17**), carbofuran (**18**), aminocarb (**19**) and methomyl (**20**) (Figure 3).

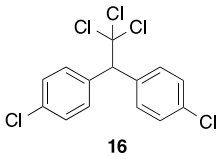


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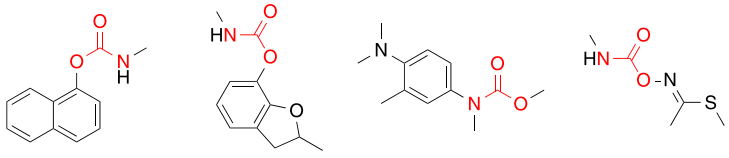
Figure 2. Molecular structure of dichlorodiphenyltrichloroethane (DDT, **16**).

Since carbamates are compounds structurally similar to acetylcholine, they serve as potent inhibitors and formidable insecticides. Methylcarbamates derived from substituted phenols and oximes, designed to fit perfectly into active site of the enzyme, generally exhibit robust AChE inhibitory properties.[41] However, it is crucial to acknowledge that by inhibiting cholinesterase, carbamates are regarded as potential carcinogens and mutagens. Therefore, the gradual adoption of carbamate pesticides introduces potential risks to both the environment and human health.[42] Pesticides containing carbamate toxicants such as carbofuran (**18**) has been widely utilized due to their anticholinergic attributes and relatively low persistence in the environment.[43]

The use of pesticides to control and eradicate pests and the increase in crop productivity in recent decades have been linked to the widespread use of these chemicals without regulation or effective implementation.[44] Many pesticides banned in the United States, Europe and Canada due to recognized threats to human health are still used or persistently employed in certain underdeveloped and in development countries.[45] For more than half a century, organophosphates have found extensive use as insecticides on a global scale. However, their usage has decreased in the past twenty years, mainly due to the increasing adoption of carbamate insecticides and the imposition of definitive limitations or bans on them in several nations. Consequently, the global spotlight has turned to carbamate pesticides.[46] This increased focus has contributed to a rise in instances of acute poisoning resulting from deliberate or inadvertent contact with these compounds. In Table 1, carbamate insecticides are categorized based on their respective relative toxicity.[47] Moreover, the challenge of developing analytical methods persists due to the low concentrations of carbamate pesticides.[48] The excessive application of pesticides has led to extensive and persistent human exposure, such as aldicarb and methomyl, and it has been associated with severe cases of human poisoning, particularly in rural areas.[47] Routes of long-term exposure include transport of pesticides from treated fields to nearby



17 18 19 20

Figure 3. Some carbamate pesticides: carbaryl (**17**), carbofuran (**18**), aminocarb (**19**) and methomyl (**20**).

Table 1. Relative toxic potency of the main carbamate pesticides (estimated human values)[47]

High toxicity (LD_{50} < 50 mg kg^{-1})	Moderate toxicity (LD_{50} = 50-200 mg kg^{-1})	Low toxicity (LD_{50} > 200 mg kg^{-1})
Aldicarb	Bufencarb	BPMC
Aldoxicarb	Carbosulfan	Carbaryl
Bendiocarb	Pirimicarb	Isoprocarb
Carbofuran	Promecarb	MPMC
Dimetan	Thiodicarb	MTMC
Dimetilan	Trimethacarb	XMC
Dioxacarb		
Formetanate		
Methiocarb		
Methomyl		
Oxamyl		
Propoxur		

LD_{50}: median lethal dose, dose at which 50% of test subjects would die from exposure; BPMC: 2-*sec*-butylphenyl methylcarbamate; MPMC: 3,4-dimethylphenyl methylcarbamate; MTMC: 3-methylphenyl methylcarbamate; XMC: 3,5-dimethylphenyl methylcarbamate.

homes or schools, inadvertent transport of pesticides home by workers, and ingestion of contaminated food and water. Another problem relates to the lack of comprehensive public health surveillance and monitoring systems to track pesticide use and associated diseases.[49]

In the environment, pesticides undergo degradation due to various factors, including chemical, biological, and physical influences. These substances can be subject to volatilization, adsorbed by soil colloids, or transported through soil leaching and surface runoff. Subsequently, they may accumulate in sediment or permeate into drainage systems.[50] The process of pesticides leaching from agricultural soil significantly contributes to groundwater contamination, while the sediments transported by surface runoff are destined for aquatic systems. The persistence of carbamates varies from 3 to more than 50 weeks, influenced by environmental factors such as soil pH and sunlight exposure. Additionally, higher temperatures can accelerate their degradation process.[51] Compared to organophosphates and organochlorines, carbamates have shorter half-lives in the environment. Climate change effects constitute an additional concern that necessitates attention, as they compound the health hazards originating from pesticide exposure within the population. This arises from heightened chemical toxicity, accelerated rates of chemical degradation, deposition of aerial pesticides onto surfaces, increased volatilization of pesticides into the atmosphere, and changes in the frequency and volume of pesticide application.[52]

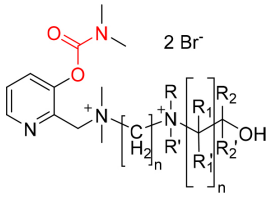
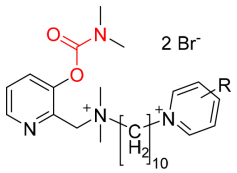
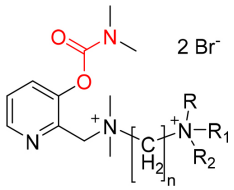
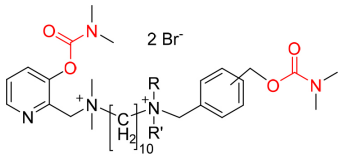
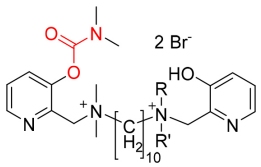
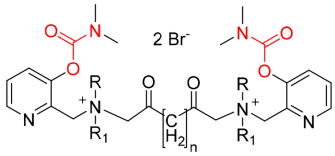
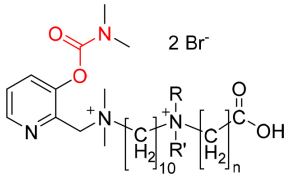
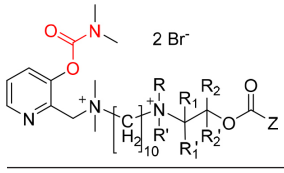
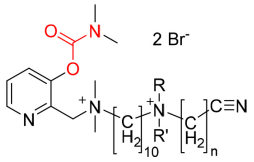
5. Carbamate Nerve Agents (CBNAs)

Carbamate Nerve Agents (CBNAs) exhibit unique characteristics that make them suitable for deployment as chemical warfare agents, owing to their exceptionally elevated toxicity across multiple pathways of contact. Their intrinsic hydrophobic nature suggests they are susceptible to absorption through skin and ocular contact, inhalation, and even oral ingestion, resulting in a grave risk that could culminate in fatality within mere minutes.[11] While CBNAs share certain resemblances with carbamate pesticides and anticholinesterase drugs, their lethal potential might surpass these comparisons by a substantial margin. Besides their utilization in various commercial sectors including medicine and agriculture, carbamates have been subject to research as plausible chemical warfare agents since the 1940s.[10] During the 1970s and 1980s, the United States Army, acting on behalf of the U.S. government, granted 23 unique U.S. patents (including two instances of duplicated patents).[53-77] These patents elucidated the synthesis procedures and fundamental toxicity evaluations (including median lethal dose (LD_{50}) measurements after intravenous injection) of chemical nerve agents that featured the integration of mono and bisquaternary ammonium functional groups (Table 2). Each patent included a myriad of compounds, attributed to the varied selection of substituents and anions during their synthesis, likely pursued to explore the relationship between structural variations and their resultant activities. It is reasonable to assume that the total number of compounds covered by these patents could easily surpass 400. The motivation behind investigating these compounds was purportedly linked to their potential as nerve-blocking agents, intended for applications such as muscle relaxants and anesthesia within the realm of medical research. However, none of the patents assert any claims about potential therapeutic advantages. Instead, all the patents explicitly point to the potential of compounds in the context of Chemical Warfare Agents (CWA).

In November 2019, during the Twenty-Fourth Session of the Conference of States Parties (CSP-24) to the Chemical Weapons Convention (CWC) of the Organization for the Prohibition of Chemical Weapons (OPCW), new compounds were introduced into Schedule 1A of the Annex on Chemicals on CWC for the first time in history.[12] All recent additions may be regarded as potential cholinesterase inhibitors, categorized as nerve agents. These compounds can be classified into two distinct groups: a pair of organophosphate compound families, a specific phosphonamidofluoride, and two separate carbamate families (Table 3). The recently scheduled carbamates comprise two amino groups carrying positive charges, with one carbamate moiety for quaternaries and two carbamate moieties for bisquaternaries, correspondingly. Nevertheless, the inclusion covered only two carbamate families, omitting various other carbamates that had previously undergone assessment for their potential in chemical warfare. The rationale behind this addition could have been to spotlight the entire class of compounds, analogous to how ricin and saxitoxin stand as representatives of toxins within the Schedule of the CWC. Similar to the chemical compounds enumerated in Schedule 1A, the quaternary and bisquaternary carbamates included in the schedule lack established commercial applications and have not been employed explicitly as weaponry.

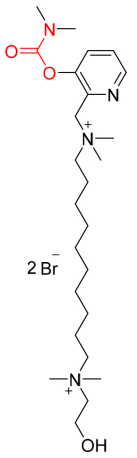
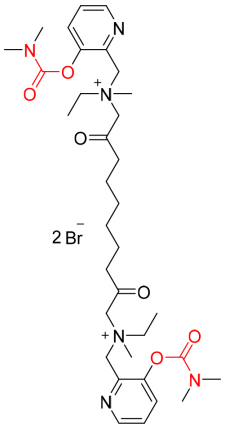
An additional aspect pertains to the limited presence of scientific literature regarding these chemical entities. Notably, carbamates stand out for their remarkable differences, both in chemical composition and toxicological effects, when compared to other developed nerve agents. Furthermore, in order to obtain data on the properties and risks of these carbamates, one often ends up comparing

Table 2. Some quaternary and bisquaternary carbamates with their LD_{50} values for intravenous injection (i.v.) mice and rabbit.

Compound	Substituent	Toxicity i.v. injection / (μg kg^{-1})		Reference
		LD_{50} mice	LD_{50} rabbits	
	R R, R'= CH_3; R_1, R_1', R_2, R_2' = H; n = 1	9	4.5	59
	R, R' = CH_3; R_1, R_1', R_2, R_2' = H; n = 2	3.6	5.6	
	R = CH_3; R' = $(CH_2)_2OH$; R_1, R_1', R_2, R_2' = H; n = 1	14	5.4	
	R = H	13	7	57
	R = CHNOH	18	5.8	
	R, R_1, R_2 = CH_3; n = 10	22	7	60
	R, R_1, R_2 = CH_3; n = 8	14	7	
	R, R' = CH_3	18	8	58
	R, R_1= CH_3	22	5.8	61
	R, R_1 = CH_3; n = 6	7	2.7	62
	R, R_1 = CH_3; n = 4	10	2.7	
	R = CH_3; R_1 = C_2H_5; n = 6	10	4	
	R, R_1 = CH_3; n = 1	32	17	63
	R, R' = CH_3; R_1, R_1' =H; R_2= H; R_2' = CH_3; Z = CH_3	13	6.3	64
	R, R' = CH_3; R_1, R_1', R_2, R_2' = H; Z = $(CH_2)_2CH_3$	13	6	
	R, R' = CH_3; n = 1	10	5.6	69
	R, R' = CH_3; n = 3	11	5.6	

LD_{50}: median lethal dose, dose at which 50% of test subjects would die from exposure.

Table 3. Carbamate families added in Schedule 1A of the CWC

Chemical name	CAS number	Structure (e.g.)
Quaternaries of dimethylcarbamoyl oxypyridines: 1-[*N*,*N*-dialkyl (≤ C10)-*N*-(n-(hydroxyl, cyano, acetoxy)alkyl (≤ C10)) ammonio]-n-[*N*-(3-dimethyl carbamoxy-α-picolinyl)-*N*,*N*-dialkyl (≤ C10) ammonio]decane dibromide (n = 1-8) e.g.,1-[*N*,*N*-dimethyl-N-(2-hydroxy)ethylammonio]-10-[*N*-(3-dimethylcarbamoxy- α-picolinyl)-*N*,*N*-dimethylammonio] decanedibromide	77104-62-2	
Bisquaternaries of dimethylcarbamoyl oxypyridines: 1,n-bis[*N*-(3-dimethylcarbamoxy-α-picolyl)-*N*,*N*-dialkyl (≤ C10)ammonio]- alkane-(2,(n-1)-dione)dibromide (n = 2-12) e.g., 1,10-bis[*N*-(3-dimethylcarbamoxy-α-picolyl)-*N*-ethyl-*N*-methylammonio] decane-2,9-dione dibromide	77104-00-8	

CWC: Chemical Weapons Convention; CAS: Chemical Abstract Service; e.g.: example given.

them with carbamates pesticides or pharmaceuticals. Some drugs that can be used for comparative purposes (Figure 4):

(*i*) Tubocurarine (**21**): this compound has a dual quaternary ammonium functional group configuration, which attaches to the nicotinic acetylcholine receptor, effectively obstructing acetylcholine binding. Tubocurarine was the pioneering compound recognized for inducing muscle paralysis through targeted action on the nicotinic acetylcholine receptor. Differing from acetylcholine, the binding of tubocurarine does not initiate the opening of membrane channels.[78]

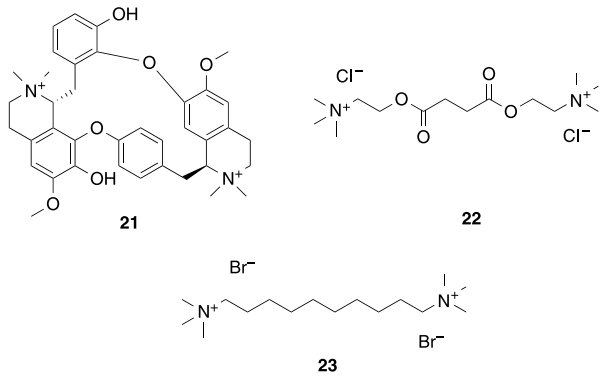


Figure 4. Some drugs with quaternary and bisquaternary ammonium centers.

(*ii*) Succinylcholine (**22**): comprising two acetylcholine molecules joined together in reverse orientation, succinylcholine binds to both acetylcholine binding sites on acetylcholine receptors. This interaction prompts channel opening, enabling cation migration. As a result, succinylcholine triggers depolarization of the neuromuscular endplate. In contrast to typical acetylcholinesterase, succinylcholine is not hydrolyzed by this enzyme. Instead, its hydrolysis is carried out by butyrylcholinesterase, operating at a slower rate.[79]

(*iii*) Decamethonium (**23**): this compound features a structural trait with two quaternary ammonium centers separated by ten methylene groups ($-CH_2$), offering significant flexibility. This flexibility permits simultaneous binding of acetylcholine to both binding sites, leading to nerve depolarization.[80]

CBNAs are class of CWAs with high lethality, attributable to their possession of quaternary ammonium and aromatic rings. Its toxicological effects are comparable to those of organophosphate nerve agents (OPNAs) such as VX.[10] Due to their ammonium groups, these compounds show a greater affinity to bind to muscarinic or nicotinic acetylcholine receptors. Furthermore, they display the ability to interact with esterases and enzymes, preventing their involvement in biological processes.[81] The mechanism of toxicity involves binding to AChE and impeding acetylcholine degradation. CBNAs exert a profound impact on the nervous system, resulting severe consequences, as delineated in the Table 4.[81] CBNAs possess the capacity to induce pathophysiological effects that disturb or hinder the regular transmission of neuromuscular impulses, even when administered in low dosages.[7] Analogous to OPNAs, CBNAs may act as AChE inhibitors. They interfere with AChE activity by carbamoylation its active site, resulting in the transfer of a carbamate group to the hydroxyl group of the serine residue. In contrast to OPNAs, whose AChE inhibition occurs through covalent modification of the serine active site with a phosphonate, phosphoamidate or phosphate group (Scheme 12).[82] Normally, the inhibition caused by OPNAs is irreversible due to slow spontaneous dephosphorylation and rapid dealkylation (referred to as "aging"). However, if an AChE reactivator such as pralidoxime (2-PAM, **24**, Figure 5) is administered immediately after exposure, the inhibition can be reversed.[83] CBNAs, on the other hand, inhibit AChE in a "pseudo-irreversible" way. The resulting carbamoyl serine is relatively weak, and undergoes moderately rapid spontaneous hydrolysis by water, with a half-life of several hours that varies depending on the specific carbamate and subsequent restoration of cholinesterase activity. The rate of decarbamoylation can be accelerated by adding an oxime.[84] Once AChE is reactivated, the degraded carbamate molecule loses its ability to inhibit the enzyme. However, depending on their structural variations, quaternary and bisquaternary compounds can impede the impulse transmission mechanism in several ways, giving rise to varied pathophysiological effects. The permanent positive charge characterizing quaternary carbamates limits their ability to traverse biological membranes, including BBB.[7] The involvement of these compounds in non-covalent interactions, such as cationic interactions and hydrogen bonds, similar to carbamates used in medical applications, remains enigmatic.

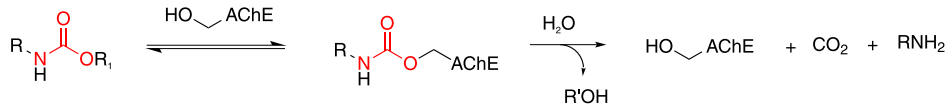
In addition to AChE inhibition, significant secondary targets include several serine hydrolase enzymes and acetylcholine receptors (AChRs). These side effects of AChE inhibitors on these targets are associated with the non-cholinergic effects exhibited by these compounds. An excellent illustration is pyridostigmine bromide (PB, **5**), an AChE carbamate inhibitor, whose adverse effects have tentatively been linked to the development of Gulf War Syndrome.[37] However, it is crucial to recognize that there is an ongoing debate and discussion about the veracity and implications of these observations.

According to US patents from the 1970's and 1980's,[53-77] there are a lack of information regarding the pharmacokinetics and toxicokinetics of these compounds, as absorption, distribution, metabolism, or elimination via diverse exposure routes, including dermal contact, inhalation, or oral ingestion. Owing to the positive charges exhibited by these compounds, they could encounter challenges in traversing membranes when absorbed through the gastrointestinal tract or via dermal contact, thereby impeding their access to the systemic circulation. Consequently, the ability of these compounds to reach nicotinic and/or muscarinic acetylcholine receptors might be compromised. However, there is a unique report of intoxication induced by hexamethonium (**25**, Figure 6),

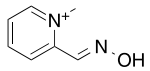
Table 4. Clinical manifestations of organophosphate *vs*. carbamate poisoning[81]

	Organophosphate intoxication	Carbamate intoxication
Central nervous system signs	common; agitation, confusion, seizures, coma, respiratory arrest	rare
Nicotinic signs	less frequent; muscular twitching, fasciculations, muscle weakens including the respiratory muscles, paralysis, tachycardia, hypertension	common; as in organophosphate poisoning
Muscarinic signs	miosis, salivation, sweating, lacrimation, rhinorrhea, abdominal cramping, vomiting, urinary incontinence, diarrhea, bronchospasm, dyspnea, hypoxemia, bradycardia, bronchial secretions, pulmonary edema and respiratory failure	as in organophosphate poisoning
Laboratory findings	AChE inhibition may be prominent weeks after intoxication	AChE inhibition noticed hours after intoxication
Delayed symptoms	intermediate syndrome, delayed neuropathy or neuropsychiatric effects are common	rare

AChE: acetylcholinesterase.



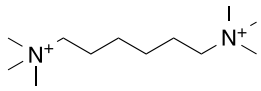
Scheme 12. Reversible inhibition of AChE by carbamates.



24

Figure 5. Chemical structure of pralidoxime (**24**).

a bisquaternary ammonium salt with a double positive charge, following inhalation exposure. The affected person underwent a progressive deterioration in lung function after inhaling a hexamethonium aerosol and despite clinical efforts, the individual tragically succumbed to the effects of exposure a month later.[85] This case suggests the potential for these agents to exhibit toxicity when inhaled via an aerosol formulation. An additional concern is that the available literature lacks details regarding the methodology for obtaining the values, the duration of animal exposure, or the associated medical symptoms. Furthermore, all documented values are obtained via intravenous injection, a method that fails to accurately mirror probable human exposure in the event of a potential attack where ingestion, dermal contact or inhalation would constitute the main exposure pathways. To comprehensively address these gaps, further toxicological investigations are imperative, encompassing assessments of toxicity at sublethal doses and thorough observation of associated symptoms.



25

Figure 6. Chemical structure of hexamethonium (**25**).

Another information regarding US patents, is that there is enough detailed data for synthesis and purification of CBNAs. The chemical processes employed in the synthesis of these compounds are relatively uncomplicated. Normally involving the combination of two precursors, an alkyl bromide with a tertiary amine in the presence of an appropriate solvent, allowing the components to undergo a simple displacement nucleophilic reaction. After a suitable reaction period, the bulk of the reaction mixture is concentrated, treated with decolorizing charcoal, filtered and subsequently induced to precipitate or form crystals. Various techniques, such as the addition of a less polar solvent and lower temperatures, can be employed to encourage precipitation or crystallization of the compound from the solution. The level of detail discussed in these patents is substantial enough for a proficient chemist to readily perform the synthesis and purification of these compounds in a controlled environment such as a glove box. This approach effectively minimizes exposure of the chemist to these highly toxic substances.

6. Final Remarks

Carbamates exemplify the intricate interplay between chemical innovation, medical progress, agricultural efficiency, and environmental consequences. Their pivotal functions in both medical and agricultural sectors bring substantial benefits, yet their intrinsic capacity for harm underscores the urgency for informed utilization, stringent regulatory supervision, and ongoing research endeavors. This combined approach aims to establish a nuanced equilibrium between human well-being and ecosystem health. The multifaceted nature of carbamates illuminates the complex landscape of modern chemical applications, reinforcing the imperative of well-informed decision-making to chart a sustainable path forward. Ultimately, carbamates straddle dual roles, representing a chemical class that encompasses both potential for positive transformation and risks. Categorizing them as strictly “good” or “bad” oversimplifies their impact, which hinges on careful management. To optimize their advantages while mitigating drawbacks, it is imperative to drive comprehensive research, implement rigorous regulations, and exercise responsible practices. This strategy will usher in harmonious and sustainable coexistence with carbamates, embodying a holistic approach that embraces progress while safeguarding our world.

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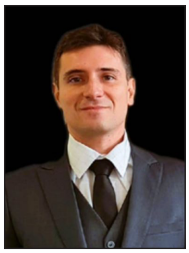

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