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HYPNOTICS AND ANTICONVULSANTS. III. CARBAMATES OF TERTIARY ACETYLENIC CARBINOLS

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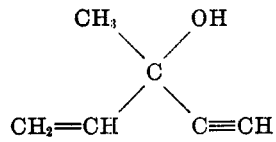
We have been interested for some time in tertiary acetylenic carbinols as central nervous system depressants (1). The long-known hypnotic activity of certain simple carbamates (2) and the recent appearance of the new drug, 1-ethynylcyclohexyl carbamate[1] (3) have now prompted us to prepare the carbamates of a number of our tertiary acetylenic carbinols.

Many of the simpler methods for preparing carbamates fail with tertiary carbinols, owing mainly to the ease of dehydration. Our preliminary experiments were carried out with methyl vinyl ethynyl carbinol (I), a representative example of the type of carbinol in which we have been interested. The highly unsaturated nature of this carbinol would be expected to lead to additional complications, and it is not surprising that all of the methods tried initially were unsuccessful.



I

Treatment of I (in excess) with cyanic acid (from cyanuric acid) gave chiefly the allophanate; although a small amount of carbamate may have been formed, we were unable to separate it from the less soluble allophanate. Reaction of I with potassium cyanate and acetic acid led apparently to extensive dehydration or rearrangement, and no carbamate could be isolated. Ester interchange between I and ethyl carbamate (urethan) in the presence of sodium ethoxide was slow and incomplete, and no carbamate of I could be detected in the recovered ethyl carbamate. Conversion of I to the mixed carbonate with ethyl chloroformate in pyridine, and treatment of this carbonate with ammonia (gas or aqueous-alcoholic) or lithium amide led only to recovery of the carbonate. The infrared spectrum of the recovered mixed carbonate gave no indication of carbamate formation.

Two of the synthetic methods reported in the literature and well reviewed by Petersen (4) appeared to be particularly applicable to tertiary carbinols. Treatment of a pyridine solution of I (with or without benzene) with carbamyl chloride, prepared by either the old or the new method (4), led to a vigorous reaction and precipitation of pyridine hydrochloride. In a number of experiments, only the carbinol could be recovered, however. Although the yield of

[1] This compound is marketed under the name "Valamin" by Schering A. G. Berlin (West).

recovered carbinol was poor, the infrared spectra showed no trace of carbamate. In one experiment, a very small amount of solid was isolated, but this proved to be the allophanate of I. The other method, which is claimed to be successful with simple tertiary alcohols (5), involves conversion of the carbinol to its chloroformic ester with phosgene at low temperature and in the presence of a tertiary amine, followed by treatment of the chloroformate with ammonia. In numerous experiments this method was applied to I and to related carbinols. In no case was there a substantial precipitate of amine hydrochloride, even at considerably higher temperatures than those recommended (−20 to −10°). Some carbinol was always recovered, but no more than a trace of carbamate could be detected after treatment with ammonia (aqueous or gaseous).

The statement is made by Petersen (4) that phenyl carbamate undergoes alcoholysis especially readily, with elimination of phenol. When a solution of phenyl carbamate in I was refluxed (150°) for several hours, there was no evidence of exchange, and the phenyl carbamate was recovered in essentially pure condition. However, this suggested a trial of what would appear to be a much more favorable process—the ammonolysis of the phenyl carbonate of I. The mixed carbonate was prepared from I and phenyl chloroformate in pyridine, and the distilled carbonate was treated with ammonia (gas). Carbamate formation was indicated by infrared spectrum, and a substantial amount of the crystalline carbamate was indeed isolated.

This process proved to be a practicable route to the carbamates of a number of tertiary acetylenic carbinols (1). It was unnecessary and in some cases undesirable due to decomposition to distil the intermediate phenyl carbonate of the carbinol. Treatment of an ether solution of the crude mixed carbonate with gaseous ammonia, alcoholic ammonia, or liquid ammonia was effective. The liquid ammonia procedure gave the best yields and cleanest products and was used in the preparation of most of the carbamates. Phenol was removed from the reaction mixture by extraction with dilute alkali, and the carbamates then were crystallized directly. Yields varied considerably, from 6.5% to 71.6%, but in most cases no attempt was made to improve the yield. The chemical properties of the nine carbamates prepared by this new method are summarized in Table I.

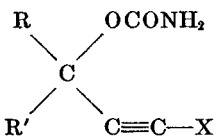
The carbamates were evaluated in mice for their hypnotic and anticonvulsant activities by procedures described elsewhere (6); pharmacological data for the carbamates and for the parent carbinols are presented in Table I. Carbamate formation does not appear to have any consistent effect on activity or on toxicity.

EXPERIMENTAL

Carbamates of tertiary acetylenic carbinols. General procedure. To a well-stirred, ice-cooled solution of 0.10 mole of the tertiary carbinol in 40 ml. of dry pyridine is slowly added 15.6 g. (0.10 mole) of phenyl chloroformate. The reaction mixture is stirred for three hours at room temperature and then decomposed by addition of 100 ml. of cold water. This mixture is extracted several times with ether, and the ether extracts are washed successively with 200 ml. of 1:1 hydrochloric acid (in two equal portions), 100 ml. of saturated sodium bicar-

TABLE I

CARBAMATES OF TERTIARY ACETYLENIC CARBINOLS



R	R′	X	Yield, %	M.P., °C.	Formula	Analyses						HD_{50}[a] mg/kg	LD_{50}[a] mg/kg	TD_{50}[a] mg/kg	ED_{50}[a]	
						Calc'd			Found						MES[b] mg/kg	Metrazole mg/kg
						C	H	N	C	H	N					
CH_3	C_2H_5	H	21.2	55.8–57	$C_7H_{11}NO_2$	59.55	7.85	9.92	59.40	7.75	9.67	195 (250)[d]	~400[c] (700)	80 (175)		28 (78)
CH_3	CH_2=CH	H	71.6	56.6–57.5	$C_7H_9NO_2$	60.42	6.52	10.07	60.41	6.60	10.16	~250 (376)	<300[e] (1100)	88 (199)	89	130 (86)
C_2H_5	CH_2=CH	H	55.2	38.2–38.8	$C_8H_{11}NO_2$	62.72	7.24	9.15	62.46	7.12	9.16	118 (179)	~450 (690)	46 (60)	~20	20 (53)
i-C_3H_7	CH_2=CH	H	25.0	44.5–45.5	$C_9H_{13}NO_2$	64.65	7.83	8.38	64.41	7.72	8.43	82 (150)	410 (340)	44 (44)	73	22 (38)
CH_3	C_2H_5	Cl	16.8	98–99	$C_7H_{10}ClNO_2$	47.87	5.74	7.98	47.94	5.79	8.00	~200 (145)	~150 (590)	~100 (64)		>100[e] (55)
CH_3	ClCH=CH	H	48.3	92.9–93	$C_7H_8ClNO_2$	48.43	4.65	8.07	48.25	4.70	8.07	92 (~150)	152 (~400)	44 (~50)	>75[e]	23 (<50[e])
C_2H_5	ClCH=CH	H	65.8	100–101.2	$C_8H_{10}ClNO_2$	51.21	5.37	7.47	51.43	5.40	7.42	90 (92)	370 (240)	34 (30)	67 (70)	12 (12)
n-C_3H_7	ClCH=CH	H	31.2	63.9–64.8	$C_9H_{12}ClNO_2$	53.60	6.00	6.95	53.62	6.11	6.93	~200 (~200)	~500 (~500)	~50 (~50)		>50[e] (~50)
i-C_3H_7	ClCH=CH	H	6.5	91–92	$C_9H_{12}ClNO_2$	53.60	6.00	6.95	53.61	5.90	7.17	150 (108)	~400 (~250)	~75 (30)	(~100)	19 (24)

[a] The pharmacological data were obtained in mice by subcutaneous injection; details of the methods used and definitions of the standard terms HD_{50}, LD_{50}, TD_{50}, and ED_{50} will be found in Ref. 6. [b] MES = maximum electroshock seizure. [c] The symbol ~ used here and elsewhere in the table indicates an estimate based on a limited amount of screening data. [d] This and all other numbers in parentheses represent the value for the corresponding carbinol. [e] The signs > and < indicate that insufficient data were available above and below the given level, respectively, for more precise estimation.

bonate, and saturated sodium chloride solution. The combined ether extracts are dried with magnesium sulfate and concentrated to a volume of 200 ml.

This ether solution of the crude mixed carbonate is added with stirring to an equal volume (200 ml.) of liquid ammonia. The mixture is stirred at the reflux temperature (Dry-Ice condenser) for 6–8 hours and then left to evaporate overnight. Ether and water are added, and the ether layer is separated and washed successively with 200 ml. of 4% sodium hydroxide (in two equal portions) and 100 ml. of saturated sodium chloride solution. The dried ether solution is concentrated to a low volume and the carbamate is crystallized by the addition of petroleum ether. The carbamate is purified by recrystallization, usually from a mixture of ether and petroleum ether.

SUMMARY

The carbamates of nine tertiary acetylenic carbinols have been prepared by a new method involving conversion of the carbinols to their phenyl carbonates with phenyl chloroformate, followed by treatment of the crude carbonates with ammonia.

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