any technique involving the use of phosphorus halides for conversion of sulfonic acids to their sulfonyl halides.

5. This investigation is to be continued in this Laboratory.

NEW HAVEN, CONN. RECEIVED APRIL 13, 1936

[CONTRIBUTION FROM THE ABBOTT LABORATORIES]

Some Alkyl and Aryl Amides and Ureides as Hypnotics[1]

BY E. H. VOLWILER AND D. L. TABERN

A considerable number of simple and substituted acetamides and acetyl ureas have been prepared from time to time and subjected to pharmacologic study. Many have been found to possess distinct hypnotic activity, and at least five, Adalin (bromodiethylacetyl urea), Neodorm (isopropylethylacetamide), Bromural (bromo-isovaleryl urea), Sedormid (allylisopropylacetyl urea), and Novonal (diethylallyl acetamide), are employed in medical practice. In their properties, these compounds appear to stand intermediate between the comparatively powerful barbiturates and the milder bromides, being chiefly used as sedatives in neuropsychic disorders.

Recent studies in the field of barbiturate hypnotics have demonstrated that certain members, particularly those containing secondary amyl groups in addition to ethyl or allyl, possess unique properties. The member most extensively investigated clinically, ethyl-1-methylbutylbarbituric acid, has been found to be characterized by its unusual rapidity of action, and by the fact that while its hypnotic action is intense, it disappears quite rapidly. As has been repeatedly pointed out,[2] this rapidity of recovery from depressant effects, is a valuable property when the drug is to be used as a preanesthetic sedative. Again, clinical reports indicate that in certain of these higher members, the sedative as contrasted to the true hypnotic properties seem to be accentuated.

It seems desirable, therefore, to prepare a series of acetyl ureas and acetamides, and the bromo analogs, containing the 1-methylbutyl and other similar secondary alkyl groups, in order to see whether the typical properties just enumerated are retained.

(1) The material covered in this paper was presented in part at the Cleveland meeting of the American Chemical Society, September, 1934, and in part at the New York meeting, April, 1935.

(2) (a) Barlow, *Arch. Surg.*, **29**, 527 (1934); (b) Waddy, "The Fear of Anaesthesia," Thesis, University of Manchester, 1934.

Experimental

The requisite malonic esters were prepared in the usual way, in absolute alcohol, employing the respective alkyl bromides (in the case of the diethylcarbinyl derivatives the *p*-toluene sulfonyl ester was utilized), and purified by fractionation.

Certain of the higher esters were very difficult to hydrolyze, prolonged refluxing with 40% potassium hydroxide in dilute alcohol being necessary. After removing the alcohol *in vacuo*, the solid mass was dissolved in cold water and carefully neutralized with hydrochloric acid until permanently acid to congo, the organic acids extracted with ether, heated to eliminate carbon dioxide, and distilled *in vacuo*. Bromo acids were synthesized essentially according to the method of "Organic Syntheses."[3]

The acetic acids were then converted to the acid chlorides by a 10% excess of thionyl chloride at room temperature and purified by fractionation *in vacuo*. No attempt was made to secure highest purity.

For the preparation of the amides, a solution of ammonium hydroxide saturated at 10° was prepared and the acid chlorides gradually dropped in at this temperature, or below, ammonia concentration being maintained by passage of a slow stream of ammonia gas. After several hours of stirring, the solid was filtered off, dried and recrystallized either from dilute alcohol, or a mixture of ether and petroleum ether, or in most cases both.

A generally more satisfactory method of preparing the amides lies in the use of the cyanoacetic esters.[4] For example: ethyl cyanoacetate was condensed by sodium ethylate in absolute alcohol by adding somewhat more than one mole of 1-ethylpropyl bromide ($\alpha^{20}D$ 1.4440) at below 60°. The separation of sodium bromide was rapid. Next morning the mass was heated to boiling and allowed to stand overnight. The ester boiled at 150–160° at 35 mm. This was ethylated by ethyl bromide and sodium ethylate, the reaction again proceeding readily. The ethyl-1-ethylpropylcyanoacetic ethyl ester boiled at 150–155° at 32 mm.

One hundred grams of this ester was refluxed with 100 g. of potassium hydroxide and 200 cc. water for twelve hours or longer. The solvent was distilled *in vacuo*, the cyanoacetic acid liberated by an excess of hydrochloric acid and extracted with benzene. On distillation through a tall column, carbon dioxide was evolved and the redistilled nitrile boiled at 190–200°.

(3) "Organic Syntheses," Coll. Vol. I, 1932, p. 108.

(4) See U. S. Patent 1,482,343 (1934).

Sixty grams of the nitrile was refluxed for ten to fifteen hours with 120 g. of potassium hydroxide in 600 cc. of 95% alcohol. The solvent was removed *in vacuo* and ice added. The separated and washed solid was redissolved in methanol. This ethyl-1-ethylpropylacetonitrile hydrolyzed with much more difficulty than most of the cyanides and liquid residues were therefore subjected to further hydrolytic treatment.

All halogen-free amides were colorless solids quite soluble in organic solvents, but relatively insoluble in water. α-Bromoethyl-1-methylbutylacetamide was an oil at room temperature.

We have found that sodamide or finely divided sodium in boiling benzene converts the halogen-free amides quantitatively into sodium salts which are soluble in the solvent and react readily with alkyl halides. The structure of the resultant amides was established by their synthesis from the acid chlorides and the requisite alkylamine.

These N-substituted amides are oils or low melting solids which may be distilled at 15 to 20 mm. They are quite insoluble in water but in the presence of starch or acacia are readily emulsified.

The acetyl ureas were prepared by heating the acid chlorides with a large excess (2.5 moles) of dry urea to 110–135°. After the main reaction, two layers were formed, the lower soon turning solid. After several additional hours of heating, the powdered mass was broken up under dilute alkali and finally recrystallized from dilute alcohol or another appropriate solvent. Another convenient method is to extract with boiling alcohol and pour into cold water kept permanently alkaline by sodium hydroxide. In several instances, appreciable quantities of higher melting substances, insoluble in cold ether, were formed.

A simpler but in general less satisfactory method for the preparation of the acetyl ureas is to heat a solution of the sodium salt of the appropriate barbituric acid in a sealed tube at 100° for several days, filter off the precipitated acetyl urea, and repeat the process.

TABLE I

Acetic acids	B. p. of acetic acids, °C.	Press., mm.	B. p. of acetyl chlorides, °C.	Press., mm.
Mono-1-methylbutyl	208–210	755	83–85	60
Ethyl-1-methylbutyl	225–230	755	103–108	45
			190	755
Allyl-1-methylbutyl	195–200	755	190–195	755
n-Butyl-1-methylbutyl	185–190	55	140	55
Ethyl-*n*-amyl	232–238	750	195–200	750
α-Bromo-1-methylbutyl			110–120	40
Ethyl-α-bromo-1-methylbutyl			138–150	50
Ethyl-α-bromo-*s*-butyl			130–135	50
Ethyl-2-ethylpropyl				

TABLE II

No.	Compound	Nitrogen, % Calcd.	Found	M. p., °C.
1	1-Methylbutylacetyl urea	16.3	16.48	180
2	Ethyl-1-methylbutylacetyl urea	14.0	13.79	133
3	α-Bromo-1-methylbutylacetyl urea	11.2	11.48	108–110
4	Ethyl-α-bromo, 1-methylbutylacetyl urea	10.0	7.56	Oil
5	Ethyl-*s*-butylacetyl urea	14.9	14.74	172
6	Isoamylethylacetyl urea	13.9	14.07	130
7	Allyl-1-methylbutylacetyl urea	13.1	13.20	123
8	Butyl-1-methylbutylacetyl urea	12.2	12.0	123
9	*n*-Butyl-ethylacetyl urea[a]	15.0	14.76	157
10	Phenyl-ethylacetyl urea[a]	13.5	13.69	137
11	Phenyl-allylacetyl urea	12.6	12.73	133–134
12	Ethyl-1-ethylpropylacetyl urea	14.0	13.98	148–150
13	Ethyl-1-methylbutylacetamide	8.91	9.12	97–98
14	α-Bromo-1-methylbutylacetamide	6.74	7.03	112–114
15	Allyl-1-methylbutylacetamide	8.2	8.35	90–91
16	Ethyl-α-bromo-1-methylbutylacetamide	5.95	6.2	Oil
17	Butyl-1-methylbutylacetamide	7.5	7.75	97–98
18	*n*-Amyl-ethylacetamide	8.91	8.9	96
19	Isoamyl-ethylacetamide[a]	8.91	9.0	106–108
20	Phenyl-ethylacetamide	8.6	8.7	85–87
21	Phenylallylacetamide	8.0	8.10	63
22	Ethyl-1-ethylpropylacetamide	8.91	8.89	123–125
23	Ethyl-1-methylbutyldiethylamide	6.56	6.31	Oil
24	α-Bromo-1-methylbutylmethylacetamide	6.27	6.44	90
25	Diethylmalonic acid monoallylamide	7.05	6.92	105
26	Ethyl-1-methylbutyl-N-methylacetamide	8.2	8.5	Oil
27	Ethyl-isopropyl-N-methylacetamide	9.8	10.0	72–75
28	Ethyl-1-methylbutyl-N-allylacetamide	7.1	7.3	Oil
29	Ethyl-isopropyl-N-allylacetamide	8.3	8.1	58–60
30	Ethyl-*s*-butyl-N-allylacetamide	7.65	7.4	Oil
31	Ethyl-isopropyl-N-ethylacetamide	8.9	9.0	Oil

[a] Described previously.

The distribution coefficients of three therapeutically promising members of the series were determined as previously described.[5]

TABLE III

Barbiturate	Distrib. coeff.
Ethyl-1-methylbutylacetamide	1.6
Ethyl-*s*-butylacetyl urea	1.1
Ethyl-isopropylacetyl urea	1.1

For the pharmacological studies of these compounds, we are indebted to Prof. A. L. Tatum of the University of Wisconsin. While he will re-

(5) Tabern and Shelberg, THIS JOURNAL, **55**, 328 (1933).

port the results in detail elsewhere, a few general observations may be indicated here.

The efficiencies of the compounds vary among themselves as much as five-fold, and the toxicities even more widely. Of those active in moderate dosage, particular interest would seem to attach, as had been anticipated, to ethyl 1-methylbutylacetyl urea and the corresponding amide. These have respectively safety margins of 18 and 11, as compared with a range from 2 to 5 for known barbiturates, and 6 for the commercial analog tested allyl isopropylacetyl urea (Sedormid).

In the N-alkyl series it was observed that when the N-substituent group was methyl, prolonged mild sedation was secured. When it was larger, excitement rather than sedation resulted.

A very interesting point is the relatively great analgesic action shown by certain of the amides, this being produced without a correspondingly deep hypnotic effect as in the barbiturates. There are also definite variations among individual members of the series.

Two chemically related substances, diethyl malonic mono-allyl amide and the bis (diethylamide) of ethyl-1-methylbutylmalonic acid, showed no true hypnotic action; the second produced local anesthesia and on oral administration clonic convulsions.

Conclusions

An extended series of simple and substituted alkyl amides and ureas has been synthesized in connection with a study of their use as sedatives and hypnotics. Considered in connection with the N-aryl and N-alkyl barbiturates described in a companion paper the results indicate the wide value of secondary butyl, amyl and hexyl groups in conferring to such compounds valuable therapeutic properties.

NORTH CHICAGO, ILL. RECEIVED MAY 8, 1936

[CONTRIBUTION FROM THE ABBOTT LABORATORIES, NORTH CHICAGO, ILL.]

N-Alkyl and N-Aryl Substituted Barbituric Acids[1]

BY D. L. TABERN AND E. H. VOLWILER

Although Fischer and Dilthey described several simple N-substituted barbituric acids as long ago as 1904,[2] until recently little systematic study has been made of higher homologs. Dox and his group[3] reported upon certain intermediate members of the series, but did not prepare compounds containing certain secondary butyl, amyl and hexyl groups, which in the simple barbiturates[4] and thiobarbiturates[5] have been found frequently to confer valuable therapeutic properties. Such compounds are among the most effective yet produced and are characterized by a prompt and intense action of short duration.

Apparently the early N-alkyl and aryl barbiturates did not attract attention because preliminary studies failed to reveal anything of especial interest; they are in general but little more active than the analogs derived from urea itself, and in certain members tend to produce pre-anesthetic excitement, paraplegia and convulsions rather than hypnosis.

More recently, however, 5,5-ethylphenyl-N-methylbarbituric acid has been reported to possess a somewhat specific action in epilepsy without the production of pronounced hypnosis, and another, 5,5-methylcyclohexenyl-N-methylbarbituric acid, has been found to have an extremely short but intense period of hypnotic activity. These interesting facts pointed to the need for a more careful study of promising compounds containing one or more secondary alkyl groups in the 5-position with particular reference to rapidity of onset, duration of action, degree of sedation or hypnosis, route and rapidity of elimination, etc. It also seemed of interest to prepare certain members containing secondary and tertiary groups attached to the nitrogen in position "1," none of these ever having been described.

Chemical

The thirty-five barbiturates of this series were prepared by one or more of the following methods: (1) reaction of the dialkylmalonic esters with the appropriate substituted urea in the presence of sodium ethylate at 100–110°; (2) reaction of the dialkyl cyanoacetic esters with a substituted

(1) Presented at the Kansas City Meeting of the American Chemical Society, April 16, 1936.

(2) Fischer and Dilthey, *Ann.*, **335**, 334 (1904).

(3) (a) Dox and Hjort, *J. Pharmac.*, **31**, 455 (1927); (b) Hjort and Dox, *ibid.*, **35**, 155 (1929); (c) Dox and Jones, THIS JOURNAL, **51**, 316 (1929).

(4) Volwiler and Tabern, *ibid.*, **52**, 1676 (1930).

(5) Tabern and Volwiler, *ibid.*, **57**, 1961 (1935).