## Summary

1. In the absence of oxygen, bromine does not react with neopentane at 80°.

2. Oxygen has little effect on the reaction of bromine with neopentane at room temperature. At 80° it causes a slow reaction.

3. At 50° organic peroxides have an effect on the bromination of neopentane similar to that of oxygen at 80°.

4. The bromination of *t*-butylbenzene is exclusively nuclear.

5. When treated with bromine at 150° trimethylacetic acid yields brominated hydrocarbons and 9% of trimethylacetoxytrimethylacetic acid.


CHICAGO, ILLINOIS RECEIVED MAY 29, 1941

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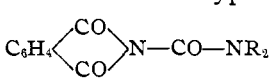
[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

# Acid Amides as Hypnotics. III. Disubstituted Acetamides

BY F. F. BLICKE AND M. F. ZIENTY[1,2]

Di- and trisubstituted barbituric acids and, to a lesser extent, acyl- and alkylureas have been the subjects of numerous publications because of the favorable properties of many of their representatives as hypnotics. Disubstituted acetamides, on the other hand, have received relatively little attention. This paper represents a continuation of our study[3] of the last-mentioned type of product and describes a number of disubstituted acetamides in which one substituent is alkyl or arylalkyl and the other alkoxyalkyl or aryloxyalkyl.

In addition to the acetamides, three derivatives of phthalimide, namely, dimethyl-, diethyl- and dibutylcarbamylphthalimide were prepared; these products are inactive as hypnotics.



We are indebted to Mr. J. W. Nelson and Dr. G. F. Cartland of The Upjohn Company for preliminary pharmacological evaluation of our products (Table II). The compounds, suspended in 5% acacia solution, were injected intraperitoneally into albino rats.

## Experimental Part

The disubstituted diethyl malonates were prepared in the usual manner from the monosubstituted esters. Compounds 1, 2, 3, 4, 5, 7 and 16 (Table I) were obtained by the use of diethyl ethylmalonate[4]; compounds 9, 10, 11, 12, 14 and 17 from diethyl β-phenylethylmalonate[5]; compound 13 from diethyl phenylmalonate[6]; compound 15 from diethyl γ-phenoxypropylmalonate[7] and compound 6 from diethyl β-benzyloxyethylmalonate.[8]

It was discovered that the use of powdered glass is distinctly advantageous in the preparation of a diethyl arylmalonate. For example, after the conversion of 1 mole of ethyl oxalate and 1.06 moles of ethyl phenylacetate into ethyl ethoxalylacetate, the addition of 40 g. of powdered glass reduced the time required for the elimination of carbon monoxide, and the formation of diethyl phenylmalonate, from five to six hours to two to three hours.

The disubstituted malonic acids, prepared by hydrolysis of the esters with alcoholic potassium hydroxide, were obtained initially as oils. Some of these crystallized rapidly, others only after a number of days.

The malonic acids were heated, in 15-g. portions, for fifteen minutes at 180° and then for one-half hour at 160°; the disubstituted acetic acids produced were distilled and converted into the acid chlorides with the aid of thionyl chloride.

The anomalous behavior of some of the acids, when heated with thionyl chloride, already has been described.[9]

The disubstituted acetamides were obtained when the acid chlorides were dropped, slowly, into an excess of strong ammonia water which was well cooled and stirred.

**β-(β'-Methoxyethoxy)-ethyl Chloride.**—To 700 g. (5.8 moles) of thionyl chloride which had been placed in a 3-l., three-necked flask, fitted with a stirrer and dropping funnel, and cooled well in a mixture of salt and ice, there was added a mixture of 63 g. (0.8 mole) of pyridine and 516 g. of β-(β'-methoxyethoxy)-ethyl alcohol[10] at such a rate that the temperature in the flask did not rise above 10°. After all of the material had been added, the flask was removed from the cooling-bath and the mixture stirred for two hours. After the addition of 100 cc. of water to dissolve the precipitated pyridine hydrochloride, the oily layer of the chloride was separated and dried with calcium chloride; b. p. 95–97° (59 mm.)[11]; yield 53%.

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by M. F. Zienty in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) The Upjohn Company Fellow.

(3) Blicke and Centolella, THIS JOURNAL, **60**, 2924 (1938).

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

(5) Dolique, *Ann. chim.*, [10] **15**, 447 (1931).

(6) "Organic Syntheses," Vol. 16, p. 34.

(7) Carther, THIS JOURNAL, **50**, 1968 (1928).

(8) Bennett and Hock, *J. Chem. Soc.*, 475 (1927).

(9) Blicke, Wright and Zienty, THIS JOURNAL, **63**, 2488 (1941).

(10) This alcohol, methyl "carbitol," was purchased from the Carbide and Carbon Chemicals Corporation; "carbitol" and butyl "carbitol" were obtained from the same source.

(11) Cretcher and Pittenger (THIS JOURNAL, **47**, 164 (1925)), found 169° (744 mm.).

TABLE I

DISUBSTITUTED MALONIC ESTERS, MALONIC ACIDS, ACETIC ACIDS AND ACETYL CHLORIDES

The malonic acids 1, 5, 7 and 15 were recrystallized from a mixture of benzene and petroleum ether (30–60°); 2 from a mixture of benzene and acetone; 3, 4, 10 and 11 from a mixture of carbon tetrachloride and petroleum ether (30–40°); 6 from carbon tetrachloride; 9 and 14 from a mixture of acetone and petroleum ether (30–40°) and 12 from benzene.

| | Malonic ester | | | | Malonic acid | | | | Acetic acid | | Acetyl chloride | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | B. p., °C. | mm. | M. p., °C. | Formula | Carbon, % calcd. | Carbon, % found | Hydrogen, % calcd. | Hydrogen, % found | B. p., °C. | mm. | B. p., °C. | mm. |
| 1 Ethyl methoxymethyl | 115–120 | 13[a] | 91–92 | $C_7H_{12}O_5$ | 47.67 | 47.53 | 6.81 | 6.92 | 115–118 | 13 | ... | .. |
| 2 Ethyl β-methoxyethyl | 135–140 | 24 | 121–122 | $C_8H_{14}O_5$ | 50.49 | 50.77 | 7.42 | 7.57 | 145–147 | 31 | ... | .. |
| 3 Ethyl β-ethoxyethyl | 155–160 | 22[b] | 81–82 | $C_9H_{16}O_5$ | 52.93 | 52.80 | 7.89 | 7.72 | 170–173 | 57[c] | ... | .. |
| 4 Ethyl β-butoxyethyl | 170–175 | 25 | 79–80 | $C_{11}H_{20}O_5$ | 56.87 | 56.80 | 8.67 | 8.71 | 145–148 | 4 | ... | .. |
| 5 Ethyl β-phenoxyethyl | 235–238 | 51[d] | 142–143 | $C_{13}H_{16}O_5$ | 61.80 | 61.84 | 6.39 | 6.56 | 210–215 | 35 | 180–185 | 35 |
| 6 Ethyl β-benzyloxyethyl | 160–165 | 2 | 80–81 | $C_{14}H_{18}O_5$ | 63.15 | 63.33 | 6.76 | 6.82 | ... | .. | ... | .. |
| 7 Ethyl γ-phenoxypropyl | 243–248 | 46 | 97–98 | $C_{14}H_{18}O_5$ | 63.16 | 63.27 | 6.76 | 6.83 | 208–210 | 20 | 185–190 | 24 |
| 8 Ethyl β-(β′-butoxyethoxy)-ethyl | 155–160 | 4 | ... | ... | ... | ... | .. | .. | 185–187 | 12 | ... | .. |
| 9 β-Methoxyethyl β′-phenylethyl | 225–230 | 31 | 143–144 | $C_{14}H_{18}O_5$ | 63.15 | 62.98 | 7.51 | 7.66 | 215–220 | 24 | ... | .. |
| 10 β-Ethoxyethyl β′-phenylethyl | 210–215 | 14 | 146–147 | $C_{15}H_{20}O_5$ | 64.24 | 64.01 | 7.04 | 7.21 | 244–248 | 54 | ... | .. |
| 11 β-Butoxyethyl β′-phenylethyl | 240–245 | 34 | 111–112 | $C_{17}H_{24}O_5$ | 66.19 | 66.35 | 7.84 | 8.07 | 226–230 | 57 | ... | .. |
| 12 β-Phenoxyethyl β′-phenylethyl | 245–250 | 2 | 188–189 | $C_{19}H_{20}O_5$ | 69.50 | 69.62 | 6.14 | 6.27 | 178–180 | 5 | ... | .. |
| 13 β-Phenoxyethyl phenyl | 208–210 | 4 | ... | ... | ... | ... | .. | .. | (m. p. 124–125) | | ... | .. |
| 14 γ-Phenoxypropyl β′-phenylethyl | 185–186 | 38 | 185–186 | $C_{20}H_{22}O_2$ | 70.13 | 70.00 | 6.01 | 6.27 | ... | .. | ... | .. |
| 15 Di-γ-phenoxypropyl | 293–296 | 11[e] | 135–136 | $C_{21}H_{24}O_6$ | 67.70 | 67.78 | 6.49 | 6.37 | 258–260 | 48 | 208–210 | 9 |
| 16 Ethyl α-phenylethyl | 173–175 | 4 | ... | ... | ... | ... | .. | .. | 165–170 | 9 | 140–150 | 12 |
| 17 *s*-Butyl β-phenylethyl | 195–198 | 12 | ... | ... | ... | ... | .. | .. | 185–190 | 17 | 175–180 | 27 |
| 18 Di-β-(β′-butoxyethoxy)-ethyl | 220–225 | 3 | ... | ... | ... | ... | .. | .. | 223–225 | 4 | ... | .. |

[a] Hill and Keach (THIS JOURNAL, **48**, 261 (1926)), b. p. 126° (18 mm.). [b] Byk (German Patent 285,636 (1915)); *Frdl.*, **12**, 709), b. p. 154–156° (19 mm.). [c] Cope and McElvain (THIS JOURNAL, **54**, 4318 (1932)), b. p. 138–139° (18 mm.). [d] Hiemenz and Taub (U. S. Patent 1,217,447); no. b. p. reported. [e] Prelog, Heimbach and Seiwerth (*Ber.*, **72**, 1321 (1936)), b. p. 245–250° (0.07 mm.).

TABLE II

DISUBSTITUTED ACETAMIDES

Compounds 1, 2, 5, 6, 7 and 9 were recrystallized from petroleum ether (90–100°); compound 3 from petroleum ether (30–60°); compounds 4 and 11 from a mixture of acetone and petroleum ether (30–60°); compound 12 from a mixture of acetone and petroleum ether (90–100°); compound 8 from carbon tetrachloride and compound 10 from benzene.

| | M. p., °C. | Formula | Nitrogen, % calcd. | Nitrogen, % found | M. L. D.[a] mg./kg. | M. H. D.[a] mg./kg. | M. L. D.[a] / M. H. D. |
|---|---|---|---|---|---|---|---|
| 1 Ethyl β-methoxyethyl | 101–102 | $C_7H_{15}O_2N$ | 9.65 | 9.82 | 500–750 | 200 | 2.5+ |
| 2 Ethyl β-ethoxyethyl | 66–67 | $C_8H_{17}O_2N$ | 8.80 | 8.94 | 1000 | 1000 | 1 |
| 3 Ethyl β-butoxyethyl | 55–56 | $C_{10}H_{21}O_2N$ | 7.48 | 7.70 | 400 | 200 | 2 |
| 4 Ethyl β-phenoxyethyl | 112–113 | $C_{12}H_{17}O_2N$ | 6.75 | 6.93 | 550 | 225 | 2 |
| 5 Ethyl γ-phenoxypropyl | 109–110 | $C_{13}H_{19}O_2N$ | 6.33 | 6.44 | 500 | 200 | 2.5 |
| 6 β-Ethoxyethyl β′-phenylethyl | 93–94 | $C_{14}H_{21}O_2N$ | 5.95 | 6.17 | 600 | 200 | 3 |
| 7 β-Butoxyethyl β′-phenylethyl | 71–72 | $C_{16}H_{25}O_2N$ | 5.32 | 5.28 | 450 | 150 | 3 |
| 8 β-Phenoxyethyl β′-phenylethyl | 119–120 | $C_{18}H_{21}O_2N$ | 4.91 | 4.87 | 2000 | 2000 | 1 |
| 9 β-Phenoxyethyl phenyl | 124–125 | $C_{17}H_{19}O_2N$ | 5.16 | 5.26 | 2000 | 2000 | 1 |
| 10 Di-γ-phenoxypropyl | 89–90 | $C_{20}H_{25}O_3N$ | 4.28 | 4.25 | 1000 | 1000 | 1 |
| 11 Ethyl α-phenylethyl | 134–135 | $C_{12}H_{17}ON$ | 7.33 | 7.66 | 450 | 125 | 3.5 |
| 12 *s*-Butyl β-phenylethyl | 112–113 | $C_{14}H_{21}ON$ | 6.40 | 6.64 | 300–500 | 150–300 | 2 + |

[a] Some estimate of the potency of the compounds can be gained by a comparison of this datum with that obtained in the case of the acylurea carbromal, $(C_2H_5)_2BrC—CO—NH—CO—NH_2$. In the latter instance the animal experiments were comparable but not identical with whose in which the acetamides were employed. Carbromal: (mg./kg.) M. L. D. 380; M. H. D. 130; M. L. D./M. H. D. 2.9.

*Anal.* Calcd. for $C_5H_{11}O_2Cl$: Cl, 25.36. Found: Cl, 25.37.

The other halogen compounds of this type were prepared in an analogous manner; to obtain the bromides, phosphorus tribromide was substituted for thionyl chloride.

**β-(β′-Ethoxyethoxy)-ethyl Chloride.**—B. p. 89–90° (28 mm.).

*Anal.* Calcd. for $C_6H_{13}O_2Cl$: Cl, 23.00. Found: Cl, 23.11.

**β-(β′-Ethoxyethoxy)-ethyl Bromide.**—B. p. 108–109° (31 mm.).

*Anal.* Calcd. for $C_6H_{13}O_2Br$: Br, 42.78. Found: Br, 42.81.

**β-(β′-Butoxyethoxy)-ethyl Chloride.**—B. p. 195–200°.[12]

*Anal.* Calcd. for $C_8H_{17}O_2Cl$: Cl, 19.44. Found: Cl, 19.39.

**β-(β′-Butoxyethoxy)-ethyl Bromide.**—B. p. 115–118° (13 mm.).

(12) Zellhoefer (*Ind. Eng. Chem.*, **29**, 550 (1937)) found 215°.

*Anal.* Calcd. for $C_8H_{17}O_2Br$: Br, 35.55. Found: Br, 35.48.

**Dimethylcarbamylphthalimide.**—Ten grams (0.11 mole) of *unsym*-dimethylurea and 22.2 g. (0.11 mole) of phthalyl chloride were heated in an oil-bath at 135° until the evolution of hydrogen chloride ceased. The mass was triturated with sodium carbonate solution and the undissolved portion recrystallized from dilute alcohol; m. p. 144–145°; yield 16 g. (70%); M. L. D. 1000; M. H. D. 1000.

*Anal.* Calcd. for $C_{11}H_{10}O_3N_2$: N, 12.84. Found: N, 12.68.

**Diethylcarbamylphthalimide.**—M. p. 116–117° after recrystallization from dilute alcohol; M. L. D. 1000; M. H. D. 600.

*Anal.* Calcd. for $C_{13}H_{14}O_3N_2$: N, 11.38. Found: N, 11.52.

**Dibutylcarbamylphthalimide.**—M. p. 179–180° after recrystallization from toluene; M. L. D. 1000; M. H. D. 1000.

*Anal.* Calcd. for $C_{17}H_{22}O_3N_2$: N, 9.27. Found: N, 9.10.

## Summary

A number of disubstituted acetamides have been described in which the substituents are alkyl, arylalkyl, alkoxyalkyl and aryloxyalkyl, and their hypnotic and lethal doses for experimental animals have been reported.

ANN ARBOR, MICHIGAN RECEIVED JULY 17, 1941

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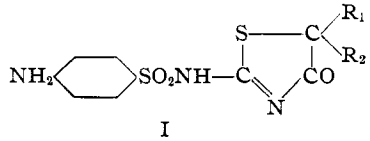
[CONTRIBUTION FROM THE MEDICAL-RESEARCH DIVISION, SHARP AND DOHME, INC.]

# Sulfonamidothiazolones*

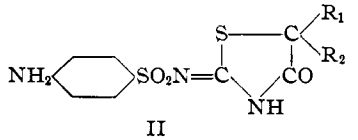
BY MAURICE L. MOORE AND CHARLES S. MILLER

In continuation of our studies of various derivatives of sulfanilamide and their chemotherapeutic activity,[1] we have prepared a series of sulfonamidothiazolones which possess considerable interest in view of the results recently reported in the synthesis and study of other heterocyclic derivatives.[2–5] We were particularly interested also in the substituted products obtained by the introduction of alkyl groups into the 5-position on the thiazolone ring. This paper describes the preparation, properties and chemotherapeutic activity of these compounds.

The acyl derivatives of 2-sulfanilamido-4-thiazolone, I or II

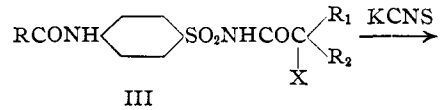


I

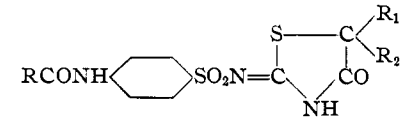


II

were prepared by the reaction of the appropriate *p*-acylaminobenzenesulfonyl chloride with the desired 2-amino-4-thiazolone in a pyridine solution or by the reaction of potassium thiocyanate with the necessary $N^4$-acyl-$N^1$-α-haloacylsulfanilamide, III, according to the equation



III



The nitro derivatives were prepared from *p*-nitrobenzenesulfonyl chloride and the 2-aminothiazolone in pyridine solution. The 2-sulfanilamido-4-thiazolones were obtained by the acid hydrolysis of the corresponding $N^4$-acetylsulfanilamidothiazolones.

These compounds are assigned structure I on the basis of Dains'[6] recent work on the stable form of some aryl-substituted 2-iminothiazolidones although Wheeler and Johnson[7] originally suggested structure II for the stable form of aryl-substituted pseudo-thiohydantoins. A study of some of the reactions of the sulfonamidothiazolones suggests that they exist in tautomeric form.

## Experimental[8]

The 2-amino-4-thiazolones used in this investigation were prepared by the reaction of the α-haloacid or α-haloacid halide with thiourea according to the usual procedures. All are reported in the literature except the following:

* These compounds may exist in tautomeric form and therefore could be called "Sulfonyliminothiazolidones."

(1) Moore, Miller and Miller, THIS JOURNAL, **62**, 2097 (1940).
(2) Foshbinder and Walters, *ibid.*, **61**, 2032 (1939).
(3) Lott, *et al.*, *ibid.*, **61**, 3593 (1939); **62**, 1873 (1940).
(4) Roblin, *et al.*, *ibid.*, **62**, 2002 (1940).
(5) Sprague and Kissinger, *ibid.*, **63**, 578 (1941).
(6) Roberts and Dains, *Univ. Kansas Sci. Bull.* **25**, 213 (1938).
(7) Wheeler and Johnson, *Amer. Chem. J.*, **28**, 121 (1902).
(8) All melting points reported are uncorrected.