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

Acid Amides as Hypnotics. I. Acylureas[1]

BY F. F. BLICKE AND A. P. CENTOLELLA[2]

The introduction of an acyl group such as diethylbromoacetyl or allylisopropylacetyl into urea converts the latter into an excellent hypnotic. Publications which illustrate the manner in which hypnotic activity varies with the nature of the acyl group are very few in number.

TABLE I

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

		Malonic ester B. p., °C.	Mm.	Malonic acid[a] M. p., °C.	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found	Acetic acid B. p., °C.	Mm.	Acetyl chloride B. p., °C.	Mm.
1	Propyl-β-phenylethyl	190–195	14	123–124	$C_{14}H_{18}O_4$	67.16	66.97	7.25	7.32	195–200	20	164–169	19
2	Isopropyl-β-phenylethyl	204–206	24	129–130	$C_{14}H_{18}O_4$	67.16	66.90	7.25	7.33	198–204	35	160–165	21
3	Allyl-β-phenylethyl	205–208	20	128–129	$C_{14}H_{16}O_4$	67.71	67.44	6.50	6.55	196–199	22	205–210	15
4	Isobutyl-β-phenylethyl	205–208	20	136–137	$C_{15}H_{20}O_4$	68.14	68.16	7.46	7.27	200–203	20	216–222	18
5	β-Cyclohexylethyl-β′-phenylethyl	255–260	30	134–135	$C_{19}H_{26}O_4$	71.64	71.36	8.24	8.24	245–250	19	220–225	25
6	Ethyl-γ-phenylpropyl	195–200	18	148–149	$C_{14}H_{18}O_4$	67.16	67.25	7.25	7.14	193–196	18	217–220	30
7	Ethyl-δ-phenylbutyl	216–220	22	114–115	$C_{15}H_{20}O_4$	68.14	68.33	7.46	7.57	227–230	50	190–194	22
8	Ethyl-ε-phenylamyl	230–235	25	106–107	$C_{16}H_{22}O_4$	69.02	69.23	7.97	7.98	213–219	20	199–204	20
9	Ethyl-ζ-phenylhexyl	227–233	18	67–68	$C_{17}H_{24}O_4$	69.83	69.56	8.28	8.19	218–222	17	206–210	21
10	Ethylcinnamyl	215–220	30	133–134	$C_{14}H_{16}O_4$	67.71	67.77	6.50	6.38	215–220	35	184–190	20

[a] The malonic acids were recrystallized from benzene.

TABLE II

SUBSTITUTED ACETYLUREAS

	Acetylurea[a]	M. p., °C.	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
1	N-Methyl-diethyl	93–95	$C_6H_{12}O_2N_2$	16.26	16.06
2	Ethyl-propyl	200–201	$C_6H_{12}O_2N_2$	16.26	16.19
3	N-Methyl-ethyl-butyl	77–78	$C_{10}H_{20}O_2N_2$	13.98	13.78
4	Ethyl-butyl-α-bromo	84–85	$C_9H_{17}O_2N_2Br$	(30.10	30.17 Br)
5	Ethyl-amyl	138–139	$C_{10}H_{20}O_2N_2$	13.98	13.91
6	Ethyl-hexyl	126–127	$C_{11}H_{22}O_2N_2$	13.06	12.70
7	Ethyl-β-cyclohexylethyl	176–177	$C_{13}H_{24}O_2N_2$	11.66	11.71
8	Di-β-cyclohexylethyl	175–176	$C_{19}H_{34}O_2N_2$	8.68	8.77
9	β-Phenylethyl	174–175	$C_{11}H_{14}O_2N_2$	13.59	13.86
10	Ethyl-benzyl	141–142	$C_{12}H_{16}O_2N_2$	12.72	13.01
11	Ethyl-β-phenylethyl	152–153	$C_{13}H_{18}O_2N_2$	11.96	11.77
12	Di-β-phenylethyl	149–150	$C_{19}H_{22}O_2N_2$	9.15	9.25
13	Propyl-β-phenylethyl	148–150	$C_{14}H_{20}O_2N_2$	11.28	11.20
14	Isopropyl-β-phenylethyl	157–158	$C_{14}H_{20}O_2N_2$	11.28	11.47
15	Allyl-β-phenylethyl	115–116	$C_{14}H_{18}O_2N_2$	11.38	11.48
16	Butyl-β-phenylethyl	117–118	$C_{15}H_{22}O_2N_2$	10.68	10.70
17	Isobutyl-β-phenylethyl	149–150	$C_{15}H_{22}O_2N_2$	10.68	10.75
18	β-Cyclohexylethyl-β′-phenylethyl	148–149	$C_{19}H_{28}O_2N_2$	8.85	8.89
19	Ethyl-γ-phenylpropyl	143–145	$C_{14}H_{20}O_2N_2$	11.28	11.68
20	Ethyl-δ-phenylbutyl	137–138	$C_{15}H_{22}O_2N_2$	10.68	10.83
21	Ethyl-ε-phenylamyl	120–121	$C_{16}H_{24}O_2N_2$	10.10	10.35
22	Ethyl-ζ-phenylhexyl	122–123	$C_{17}H_{26}O_2N_2$	9.65	9.89
23	Ethylcinnamyl	139–140	$C_{14}H_{18}O_2N_2$	11.38	11.37

[a] The compounds were recrystallized in the following manner: compounds 8, 14, 18, 20, 21 and 22 from petroleum ether (90–100°); compound 7 from alcohol; compounds 3, 4, 11 and 16 from dilute alcohol; compounds 2, 5, 6, 9 and 12 from acetone; compound 13 from 50% acetone; compounds 10, 17 and 19 from a mixture of one part acetone and two parts petroleum ether; compounds 15 and 23 from a mixture of one part acetone and nine parts petroleum ether.

In this paper we have described a number of disubstituted acetylureas, $R_2CH\text{-}CO\text{-}NH\text{-}CO\text{-}NH_2$ (Table II), which were examined pharmacologically by Mr. J. W. Nelson and Dr. G. F.

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by A. P. Centolella in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) The Upjohn Company Fellow.

Cartland in The Upjohn Company Laboratories.[3] It was quite surprising to find that none of these ureas were effective to any great degree when injected intraperitoneally into white rats although, in a second paper, it will be shown that some of the corresponding acetamides are strong hypnotics.

The ureas were obtained by the following general method: conversion of malonic ester into the required disubstituted derivative, $R_2C(CO-OC_2H_5)_2$, hydrolysis of the ester, elimination of carbon dioxide with the formation of a disubstituted acetic acid, $R_2CH—COOH$, preparation of the corresponding acetyl chloride and treatment of the latter with urea or methylurea.[4]

The new intermediates are described in Table I.

Experimental Part

The procedures are illustrated in the case of allyl-β-phenylethylacetylurea.

To sodium ethylate, prepared from 1000 cc. of absolute alcohol and 46 g. of sodium, there was added, slowly, 320 g. of malonic ester. After one hour the mixture was stirred and refluxed and 370 g. of β-phenylethyl bromide added during the course of two hours. The mixture was stirred and refluxed for two hours longer, most of the alcohol removed by distillation and 500 cc. of water added to the cold residue. The ester layer was separated and the aqueous layer extracted six times with 75-cc. portions of ether; yield of β-phenylethylmalonic ester 424 g. or 80% of the calcd. amount; b. p. 182–185° (12 mm.).[5]

In a manner similar to that described above, allyl-β-phenylethylmalonic ester was prepared from sodium ethylate, obtained from 300 cc. of alcohol and 13.8 g. of sodium, 159 g. of β-phenylethylmalonic ester and 73.2 g. of allyl bromide; yield 159 g. or 88% of the calcd. amount.

A mixture of 80 g. of potassium hydroxide, 250 cc. of 70% alcohol and 101 g. of the disubstituted malonic ester was refluxed for twenty-four hours, most of the alcohol removed, 250 cc. of water added and then about 140 cc. of hydrochloric acid added to the cold mixture. The crude acid separated from the acidic mixture as an oil but soon solidified; yield 78 g. or 94% of the calcd. amount.

Fifteen grams of the allyl-β-phenylethylmalonic acid was heated in an oil-bath at 180° until most of the carbon dioxide had been evolved and then heated at 150–160° for six hours; yield 10.7 g. or 86% of the calcd. amount.

A mixture of 28 g. of the acetic acid and 45 g. of commercial thionyl chloride was heated for two hours on a steam-bath after the initial vigorous reaction had subsided and the excess thionyl chloride then removed; the yield of acid chloride was 21 g. or 70% of the calcd. amount.

Nine grams of allyl-β-phenylethylacetyl chloride and 9.6 g. of dry urea were heated in an oil-bath at 125°. As soon as the material had melted the temperature was dropped to 110–115°. After six hours the product was cooled and rubbed in a mortar with enough 10% sodium carbonate solution to keep the mixture alkaline. The solid material was filtered, washed with water and recrystallized; yield 8.9 g. or 90% of the calcd. amount.

Summary

A number of new disubstituted malonic esters, malonic acids, acetic acids, acetyl chlorides and acetylureas have been described.

No strong hypnotics were found among the disubstituted acetylureas, $R_2CH—CO—NH—CO—NH_2$, studied.

ANN ARBOR, MICHIGAN RECEIVED OCTOBER 10, 1938

(3) Their results will be published by them in detail in another journal.

(4) Davis and Blanchard, THIS JOURNAL, **51**, 1797 (1929).

(5) Dolique [*Ann. chim.*, [10] **15**, 447 (1931)] reported 184–185° at 15 mm.

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

Acid Amides as Hypnotics. II. Acetamides[1]

BY F. F. BLICKE AND A. P. CENTOLELLA[2]

It has been known for a long time that certain representatives of three types of acid amides—substituted acetamides, acylureas and cyclic amides such as substituted barbituric acids and hydantoins—exhibit strong hypnotic activity.

During late years, due to the popularity of barbituric acid compounds, the study of the acetamide type has been neglected except for the publications of Volwiler and Tabern[3] and of Junkmann.[4]

Most of the acetamides, described hitherto as compounds which possess hypnotic action, are trisubstituted derivatives such as diethylallylacetamide. Since, in general, trisubstituted acetamides are more difficult to obtain than the disubstituted compounds we have prepared a considerable number of the latter in order to determine their activity as hypnotics.

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by A. P. Centolella in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) The Upjohn Company Fellow.

(3) Volwiler and Tabern, THIS JOURNAL, **58**, 1353 (1936).

(4) Junkmann, *Arch. exptl. Path. Pharmakol.*, **186**, 552 (1937).