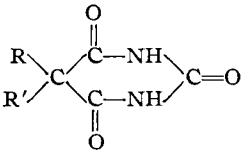
Barbituric Acids*

By ROBERT BRUCE MOFFETT,† JAMES E. STAFFORD,† and CHARLOTTE ANNE HART

In connection with other work in these laboratories (1–5) a large number of malonic esters were available, most of which had not been previously described. In order to characterize them further, it was thought desirable to prepare solid derivatives. We have, therefore, made a series of barbituric acids from most of those malonic esters by allowing them to react with urea in the presence of sodium ethoxide or sodium methoxide.

Table I records the physical properties of these barbituric acids. They were all prepared by

Table I.—Barbituric Acids



R	R′	Yield, %[a]	M. p., °C.	Empirical Formula	Analysis, % Nitrogen Calcd.	Found
n-Amyl	Δ²-Cyclopentenyl	21.	120–122[d]	$C_{14}H_{20}N_2O_3$	10.60	10.31
iso-Amyl	Δ²-Cyclopentenyl	4.5	128–133[d]	$C_{14}H_{20}N_2O_3$	10.60	10.71
2-Methylbutyl	Δ²-Cyclopentenyl	29.2	125–131[e]	$C_{14}H_{20}N_2O_3$	10.60	10.56
2-Ethylbutyl	Δ²-Cyclopentenyl	9.2	146–149	$C_{15}H_{22}N_2O_3$	10.07	9.83[b]
2-Chloroallyl	Δ²-Cyclopentenyl	9.5	183–186	$C_{12}H_{13}ClN_2O_3$	10.39	10.43
Benzyl	Δ²-Cyclopentenyl	46.8	219–221	$C_{16}H_{16}N_2O_3$	9.86	9.93
2-Cyclohexylethyl	Δ²-Cyclopentenyl	55.8	175–180	$C_{17}H_{24}N_2O_3$	9.21	9.33
2-Phenoxyethyl	Δ²-Cyclopentenyl	62.3	246–248	$C_{17}H_{18}N_2O_4$	8.92	8.96
Δ²-Cyclohexenyl	Δ²-Cyclopentenyl	24.6	183–184	$C_{15}H_{18}N_2O_3$	10.22	10.46
Cyclohexylmethyl	Δ²-Cyclopentenyl	33.7	212–214	$C_{16}H_{22}N_2O_3$	9.65	9.52
Furfuryl	Δ²-Cyclopentenyl	32.	171–173.5	$C_{14}H_{14}N_2O_4$	9.65	9.76
Cyclopentyl	Δ²-Cyclopentenyl	44.	162–165.5[f]	$C_{14}H_{18}N_2O_3$	10.69	10.15
2-Thienylmethyl	Δ²-Cyclopentenyl	41.4	208.5–209.5	$C_{14}H_{14}N_2O_3S$	9.65	9.37
2-Diethylaminoethyl	Δ²-Cyclopentenyl	44.	175–177[d]	$C_{15}H_{23}N_3O_3$	14.33	14.24
n-Propyl	Cyclopentyl	68.4	177–178	$C_{12}H_{18}N_2O_3$	11.76	11.60
n-Butyl	Cyclopentyl	36.	172–174	$C_{13}H_{20}N_2O_3$	11.11	11.18
iso-Butyl	Cyclopentyl	30.	168–172	$C_{13}H_{20}N_2O_3$	11.11	10.86
n-Amyl	Cyclopentyl	27.	[d]	$C_{14}H_{22}N_2O_3$	10.52	10.44
iso-Amyl	Cyclopentyl	15.	145–147	$C_{14}H_{22}N_2O_3$	10.52	10.23
2-Methylbutyl	Cyclopentyl	12.	131–135	$C_{14}H_{22}N_2O_3$	10.52	10.35
2-Ethylbutyl	Cyclopentyl	5.	171–173[d]	$C_{15}H_{22}N_2O_3$	9.99	9.74
2-Cyclohexylethyl	Cyclopentyl	48.3	164–166.5	$C_{17}H_{22}N_2O_3$	9.15	9.31
Benzyl	Cyclopentyl	54.	245–247	$C_{14}H_{18}N_2O_3$	10.68	10.81
Furfuryl	Cyclopentyl	43.2	190–191.5	$C_{14}H_{16}N_2O_4$	9.61	9.63
2-Thienylmethyl	Cyclopentyl	43.7	219–220	$C_{14}H_{16}N_2O_3S$	9.58	9.56
2-Diethylaminoethyl	Cyclopentyl	53.7	159–160[d]	$C_{15}H_{25}N_3O_3$	14.23	14.14
n-Propyl	Δ²-Cyclohexenyl	37.	146–148	$C_{13}H_{18}N_2O_3$	11.19	11.45
n-Butyl	Δ²-Cyclohexenyl	39.5	160–163	$C_{14}H_{20}N_2O_3$	10.59	10.71
2-Methylbutyl	Δ²-Cyclohexenyl	14.	160–162[d]	$C_{15}H_{22}N_2O_3$	10.07	9.93
2-Ethylbutyl	Δ²-Cyclohexenyl	19.6	178–179	$C_{16}H_{24}N_2O_3$	9.58	9.37
Δ²-Cyclohexenyl	Δ²-Cyclohexenyl	25.	202–213	$C_{16}H_{20}N_2O_3$	9.71	9.69
Cyclohexylmethyl	Δ²-Cyclohexenyl	35.	229–231	$C_{17}H_{24}N_2O_3$	9.21	9.25
2-Cyclohexylethyl	Δ²-Cyclohexenyl	51.8	189–193	$C_{18}H_{26}N_2O_3$	8.80	8.81
Benzyl	Δ²-Cyclohexenyl	44.1	234–239	$C_{17}H_{18}N_2O_3$	9.39	9.45
Furfuryl	Δ²-Cyclohexenyl	52.5	219–221	$C_{15}H_{16}N_2O_4$	9.21	9.34
Cyclohexyl	2-Cyclohexylethyl	34.4	210–212	$C_{18}H_{28}N_2O_3$	8.74	8.72
Cyclohexyl	Benzyl	36.7	267–269	$C_{17}H_{20}N_2O_3$	9.33	9.09
1-Hydrindenyl	Allyl	63.	168–170	$C_{16}H_{16}N_2O_3$	9.86	9.90
1-Hydrindenyl	Benzyl	31.	196–199	$C_{20}H_{18}N_2O_3$	8.38	8.34
Tetrahydrofurfuryl	Benzyl	81.6[c]	239–241	$C_{16}H_{18}N_2O_4$	9.27	9.45
Tetrahydrofurfuryl	Cyclohexylmethyl	63.	192–194	$C_{16}H_{24}N_2O_4$	9.09	9.08

[a] The yields are reported for recrystallized products. In most cases, no attempt was made to work up the filtrates.
[b] Chlorine analysis—Calcd.: Cl, 13.20. Found: Cl, 13.18.
[c] This yield is based on unrecrystallized material, m. p. 237–239°.
[d] Crystallized from 95% ethanol.
[e] Crystallized from benzene plus petroleum hexane.
[f] Crystallized from benzene.

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The functions of the George A. Breon and Company laboratories have been assumed by the Sterling-Winthrop Research Institute, Rensselaer, N. Y., and any requests for reprints should be addressed there.
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essentially the same general method which is given in the Experimental part.

EXPERIMENTAL

General Method for the Preparation of Barbituric Acids.—A mixture of 0.1 mole of the malonic ester, 0.22 mole of sodium ethoxide (or sodium methoxide), 0.13 mole of urea, and 65 ml. of absolute ethanol was refluxed for about six hours. The solvent was then removed by distillation and the residue was heated in an oil bath at 110–120° for two hours. After cooling, the mixture was thoroughly shaken with water, extracted twice with ether, and acidified with acetic acid. The barbituric acids usually separated as oils which crystallized on standing and scratching. The solid was collected on a filter, dried, and recrystallized, usually from methanol, adding a little water if necessary to secure good separation.

REFERENCES

(1) Moffett, R. B., Hart, C. A., and Hoehn, W. M., *J. Am. Chem. Soc.*, **69**, 1849(1947).
(2) Moffett, R. B., Hart, C. A., and Hoehn, W. M., *ibid.*, **69**, 1854(1947).
(3) Moffett, R. B., Hart, C. A., and Neil, J., *J. Org. Chem.*, **15**, 343(1950).
(4) Moffett, R. B., and Neil, J., *ibid.*, **15**, 354(1950).
(5) Moffett, R. B., and Hart, C. A., THIS JOURNAL, **42**, 717(1953).

The Development of Organic Iodine Compounds as X-Ray Contrast Media*

By V. H. WALLINGFORD†

A FEW YEARS AGO Rigler (1) of the University of Minnesota stated that "approximately 80 per cent of patients in hospitals and 70 per cent of those seen in outpatient clinics will be submitted to some form of roentgen study at some period in the course of their illness." That statement serves to point out the important position X-ray diagnosis has attained in modern medical practice. X-ray contrast media, including the organic iodine compounds discussed in the present paper, have played an essential role in this development.

Immediately following the discovery of X-rays in 1895 scientists attempted to use this new tool to explore the interior of the living human body, and to view structures otherwise visible only during surgery or autopsy. While the bones were clearly visualized by X-rays, other parts or organs of the body were not distinguishable because they lacked contrast with the surrounding tissues. Some visualization was attained by surrounding the soft tissues under study with dense materials such as lead shot or iron powder. Cannon (2) of the Harvard Medical School, a pioneer radiologist in this country, studied the esophagus of the goose, using a paste of bismuth salts as the contrasting agent. To hold the subject stationary enough for the comparatively long exposures required by the X-ray tubes of that day, he enclosed the neck of the goose in cardboard formed like a mailing tube. Bismuth subnitrate came into general use in 1904 (3) for the examination of the gastrointestinal tract, only to be supplanted in 1910 (4) by barium sulfate. The Mallinckrodt Chemical Works entered the field of X-ray contrast media in 1913 with the introduction of a grade of barium sulfate specially prepared for this application.

The element iodine has been found particularly useful for incorporation into X-ray contrast media. It exhibits high absorption of X-rays in the range or wave lengths applicable to the human body. Sodium iodide has long been used for cystography and even for intravenous injection. Because of its toxic side reactions and its irritant effect on mucous surfaces, however, it has been largely displaced by the organic iodine compounds. The chemical nature of iodine permits its combination into stable, nontoxic organic substances specially adapted to specific techniques of X-ray diagnosis.

IODIZED OILS

The first organic iodine compound to be used as an X-ray contrast medium was Lipiodol, introduced in 1922 (5). Chemically, this is poppy seed oil containing organically bound iodine. In the intervening years a number of iodized oils have been prepared from various unsaturated vegetable oils.

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Presented to the Scientific Section of the A. PH. A., Salt Lake City meeting, August 19, 1953, by V. H. Wallingford, recipient of the Fifth (1952) Chilean Iodine Educational Bureau Award for outstanding research in the chemistry and pharmacology of iodine.
† This work on iodine compounds has been shared by many individuals. To all of them I express my appreciation. Special thanks are due to Dr. Melvin A. Thorpe who, from the beginning, has shared my hopes and enthusiasm and has spared no effort in arranging clinical trials and caring for the many details necessary for the introduction of a new medicinal.