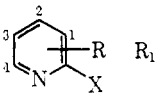
TABLE I
SYNTHETIC INTERMEDIATES

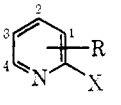


$R_1 = CH_2Br \cdot HBr$; $R_2 = CH_2C(COOC_2H_5)_2NHCOCH_3$

No.	X	R	Position	Mp, °C	Recrystn[b] solvent	Yield[d]	Formula[a]
1	Br	R_1	1	135–143 dec	*c*	15	$C_6H_6Br_3N$[e]
2	Br	R_1	2	120–124 dec	*c*	59	$C_6H_6Br_3N$
3	Br	R_1	3	160–170 dec	*c*	33	$C_6H_6Br_3N$
4	Br	R_1	4	150–157 dec	*c*	53	$C_6H_6Br_3N$[f]
5	Cl	R_1	1	98–110 dec	*c*	47	$C_6H_6Br_2ClN$
6	Cl	R_1	2	113–119 dec	*c*	71	$C_6H_6Br_2ClN$
7	Cl	R_1	3	92–98 dec	*c*	62	$C_6H_6Br_2ClN$
8	Cl	R_1	4	95–111 dec	*c*	58	$C_6H_6Br_2ClN$
9	Br	R_2	1	107–180	W	33	$C_{15}H_{19}BrN_2O_5$
10	Br	R_2	2	103–104	E–P	19	$C_{15}H_{19}BrN_2O_5$
11	Br	R_2	3	119–120	W	19	$C_{15}H_{19}BrN_2O_5$[g]
12	Br	R_2	4	81–82	W–A	30	$C_{15}H_{19}BrN_2O_5$
13	Cl	R_2	1	112–114	E	29	$C_{15}H_{19}ClN_2O_5$
14	Cl	R_2	2	106–107	E	13	$C_{15}H_{19}ClN_2O_5$
15	Cl	R_2	3	114–116	W	32	$C_{15}H_{19}ClN_2O_5$
16	Cl	R_2	4	114–115	W	45	$C_{15}H_{19}ClN_2O_5$

[a] All compds were analyzed for C, H, N. [b] A = Me_2CO, E = Et_2O, P = petr ether, W = H_2O. [c] Unstable to recrystn. [d] Yield of crude product for **1–8**; yield of purified product for **9–16**. [e] C: calcd, 21.71; found, 23.55. [f] C: calcd, 21.71; found, 22.72. [g] C: calcd, 46.52; found, 47.02.

TABLE II
BROMO- AND CHLORO-SUBSTITUTED PYRIDYLALANINES



$R = CH_2CHCOOH$ (with NH_2)

No.	X	R (position)	Mp, °C dec	Uv (λ_{max})	Recrystn[b] solvent	Yield purified, %	Formula[a,c]
17	Br	1	200–201	271	W–A	47	$C_8H_9BrN_2O_2$
18	Br	2	187–189	269	W–A	42	$C_8H_9BrN_2O_2$
19	Br	3	253–255	272	W	68	$C_8H_9BrN_2O_2$
20	Br	4	230–232	271	W	51	$C_8H_9BrN_2O_2$
21	Cl	1	200–201	270	W–A	31	$C_8H_9ClN_2O_2$
22	Cl	2	203–206	267	W–A	38	$C_8H_9ClN_2O_2$
23	Cl	3	260–262	271	W	47	$C_8H_9ClN_2O_2$
24	Cl	4	182–184	271	W–A	50	$C_8H_9ClN_2O_2$

[a] See footnote *a*, Table I. [b] See footnote *b*, Table II. [c] The bromopyridylalanines (**17–20**) did not give consistently acceptable C analyses. However, the N analyses were acceptable in every case except for **18** for which, N: calcd, 11.43; found, 11.92.

HBr at 0°. The pptd salt was rapidly filtered by suction, washed with several portions of anhyd Et_2O, and stored over P_2O_5. The product was unstable to recrystn, but was sufficiently pure (Table I) for further synthetic work.

Ethyl 2-Acetamido-2-(2-bromo-3-pyridylmethyl)malonate (Table I, 9–16).—To 1.15 g (0.050 g-atom) of Na in 150 ml of Mg-dried EtOH was added 5.43 g (0.025 mole) of ethyl acetamidomalonate. To this soln was added 8.3 g (0.025 mole) of 2-bromo-3-bromomethylpyridine·HBr and the soln refluxed until the pH of an aliquot dissolved in distd H_2O had decreased to approximately pH 5–6. The reaction mixt was taken to dryness *in vacuo*, and the product was extd (Et_2O). It was then crystd from Et_2O–petr ether and recrystd from H_2O. The condensation leading to **10**, **12**, **14**, and **16** was carried out in the same vol (as above) of 1:1 C_6H_6–EtOH. For **12** and **16** a molar excess of ethyl acetamidomalonate and Na was used, and the halide was added portionwise over a period of 1 hr. Physical constants and analyses are given in Table I.

β-(2-Bromo-3-pyridyl)-DL-alanine (Table II, 17–24).—Compound **9** (3.86 g, 0.010 mole) was hydrolyzed in the presence of 50 ml of refluxing 6 *N* HCl for 9 hr. The soln was evapd to dryness *in vacuo*, and the residue was dissolved in 100 ml of H_2O and neutralized (Amberlite IR-45). The neutralized soln was decolorized (Darco G-60) and concd to dryness *in vacuo*. The amino acid was recrystd from H_2O–Me_2CO. Physical constants and analyses are reported in Table II.

Quaternary Ammonium Salts of Tertiary Aminoalkyl Amides

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Quaternary ammonium salts derived from long-chain fatty acids are known to possess antimicrobial activity.[2] Many N-substituted amides of long-chain fatty acids have been reported to have antimycotic activity.[3–5]

(1) A laboratory of the Southern Utilization Research and Development Division, ARS, U. S. Department of Agriculture. Naming of a company or product does not imply approval or recommendation by the Department over others which may also be suitable.

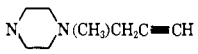
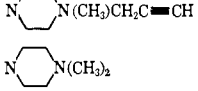
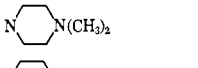
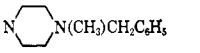
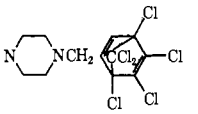
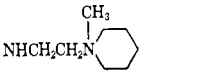
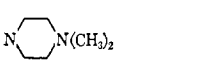
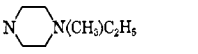
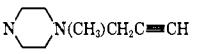
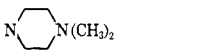
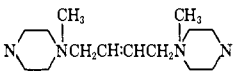
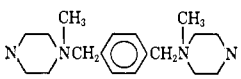
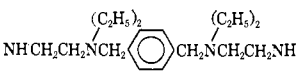
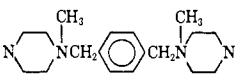
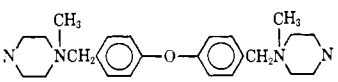
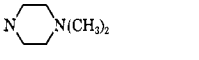
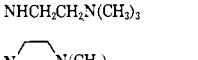
(2) R. A. Reck and H. J. Hardwood, *Ind. Eng. Chem.*, **45**, 1022 (1953).

(3) A. F. Novak, G. C. Clark, and H. P. Dupuy, *J. Amer. Oil Chemists' Soc.*, **38**, 321 (1961).

(4) A. F. Novak, M. J. Fisher, S. P. Fore, and H. P. Dupuy, *ibid.*, **41**, 503 (1964).

(5) A. F. Novak, J. M. Solar, R. R. Mod, F. C. Magne, and E. L. Skau, *ibid.*, **46**, 249 (1969).

TABLE I

No.[a]	R	X[b]	Mp, °C	Formula[c]
1	$NHCH_2CH_2N(CH_3)_3$	C	128–131	$C_{21}H_{45}IN_2O$
2	$NHCH_2CH_2N(C_2H_5)CH_3$	C	63–65	$C_{23}H_{49}IN_2O$
3	$NHCH_2CH_2N(C_2H_5)_2CH_2C{\equiv}CH$	B	107–109	$C_{25}H_{49}BrN_2O$
4	$NHCH_2CH_2N(CH_3)_2CH_2C{\equiv}CH$	B	75–78	$C_{23}H_{45}BrN_2O$
5		B	100–103	$C_{24}H_{45}BrN_2O$
6		D	127–130	$C_{23}H_{48}N_2O_5S$
7		B	147–150	$C_{22}H_{45}BrN_2O$
8		C	161–163	$C_{22}H_{45}IN_2O$
9		A	183–187	$C_{28}H_{49}ClN_2O$
10		B	144–146	$C_{29}H_{45}BrCl_6N_2O$
11	$NHCH_2CH_2N(CH_3)_3$	C	109–111	$C_{23}H_{47}IN_2O$
12	$NHCH_2CH_2N(CH_3)_2CH_2C{\equiv}CH$	B	Paste	$C_{25}H_{47}BrN_2O$
13		C	183–186	$C_{28}H_{49}ClN_2O$
14		B	Paste	$C_{24}H_{47}BrN_2O$
15		C	146–149	$C_{24}H_{47}IN_2O$
16		D	Paste	$C_{25}H_{50}N_2O_5S$
17		B	Paste	$C_{25}H_{49}BrN_2O$
18		B	Viscous liquid	$C_{26}H_{47}BrN_2O$
19	$NHCH_2CH_2N(C_2H_5)_2CH_3$	C	65–67	$C_{25}H_{53}IN_2O$
20	$NHCH_2CH_2N(CH_3)_3$	C	123–125	$C_{23}H_{49}IN_2O$
21		C	163–165	$C_{24}H_{49}IN_2O$
22		A	*d*	$C_{50}H_{94}Cl_2N_4O_2$
23		A	*e*	$C_{54}H_{96}Cl_2N_4O_2$
24		A	55–57	$C_{52}H_{100}Cl_2N_4O_2$
25		A	230–240 dec	$C_{50}H_{92}Cl_2N_4O_2$
26		A	210–212	$C_{56}H_{96}Cl_2N_4O_3$
27		C	112–114	$C_{31}H_{62}I_2N_4O_2$
28	$NHCH_2CH_2N(CH_3)_3$	C	124–126	$C_{15}H_{33}IN_2O$
29		C	151–153	$C_{16}H_{33}IN_2O$

[a] **1-10** (palmitoyl-R)X; **11-18** (oleoyl-R)X; **19-21** (stearoyl-R)X; **22-24** (oleoyl-R-oleoyl)X_2; **25** and **26** (palmitoyl-R-palmitoyl)X_2; **27** ($n + m = 15$), $[CH_3(CH_2)_nCH(COR)(CH_2)_mCOR]X_2$; **28** and **29** (decanoyl-R)X. [b] A, chloride; B, bromide; C, iodide; D, $CH_3SO_4^-$. [c] All compounds were analyzed for N, and the analytical values were within ±0.4% of the calculated values. [d] Softening with color change at 193°; 210° dec. [e] Softening with color change at 175°; 215° dec.

1,3-Diacylimidazolidines and -hexahydropyrimidines have exhibited antimycotic activity.[6] Quaternary ammonium salts of dicarboxylic acid bis(β-tertiary aminoalkyl)amides have been evaluated as curare substitutes.[7] In the course of preparing amide derivatives, various types of quaternary ammonium salts of tertiary aminoalkylamides have been prepared.

(6) R. R. Mod, F. C. Magne, G. Sumrell, A. F. Novak, and J. M. Solar, *J. Amer. Oil Chemists' Soc.*, in press.

(7) A. P. Philips, *J. Amer. Chem. Soc.*, **73**, 5822 (1951).

Experimental Section[8]

The melting points were determined on a Fisher-Johns apparatus and are uncorr.

(2-Palmitoylaminoethyl)trimethylammonium iodide was prepd by reaction of *N*-(dimethylaminoethyl)palmitamide (**I**) with MeI (II). I was prepd by the reaction of palmitoyl chloride with dimethylaminoethylamine in the usual manner. I (10 g, 0.03 mole) was dissolved in 25 ml of Et_2O, after which II (4.4 g, 0.03 mole) was added. After standing for 10 hr, the mixt was

(8) Microanalyses are by Galbraith Laboratories, Knoxville, Tenn.

centrifuged, and the white solid was recrystd twice from 1:1 Me_2CO–EtOH. The product was dried (P_2O_5) *in vacuo*.

4-Palmitoyl-1-methyl-[1,4,5,6,7,7-hexachlorobicyclo[2.2.1]-hepta-2,5-diene-2-methylene]piperazinium bromide was prepd by reaction of 1,4,5,6,7,7-hexachloro-2-bromomethylbicyclo-[2,2.1]-2,5-heptadiene (III)[9] with *N*-palmitoyl-*N'*-methylpiperazine (IV). III was prepared as previously described.[9] IV was prepd by the reaction of palmitoyl chloride with *N*-methyl piperazine in the usual manner. III (11.6 g, 0.03 mole) and IV (10 g, 0.03 mole) were allowed to react under reflux for 10 hr in 50 ml of 2,2-dimethoxypropane. The solvent was removed by stripping, after which the product was recrystd 4 times from 1:1 Me_2CO–EtOH and dried (P_2O_5) *in vacuo*.

The remaining quaternary salts were prepd by the interaction of equimolar proportions of the respective amide with the respective halide or Me_2SO_4 as described for (2-palmitoylaminoethyl)-trimethylammonium iodide.

Screening on agar plates by a method previously described[5] revealed that most of the compds in Table I showed slight to moderate activity against one or more of the following organisms: *Bacillus* sp., *Pseudomonas* sp., *Aspergillus flavus*, *Candida albicans*, *Microsporum gypseum*, *Trichophyton rubrum*, and *T. violaceum*.

Nematocidal tests of **1**, **8**, and **10** (Table I) by a previously described method[10] revealed that they had high activity against the *Penagrellus redivivus* organism, all 3 showing 90–100% kill at 100 ppm.

(9) E. K. Fields, *J. Amer. Chem. Soc.*, **76**, 2709 (1954).

(10) S. S. Block, W. H. Schuller, J. C. Minor, and R. V. Lawrence, "The Evaluation of Selected Naval Stores Derivatives as Agricultural Chemicals." U. S. Department of Agriculture, ARS 72-68, U. S. Department of Agriculture, Agricultural Research Service, Washington, D. C., 1969, p 1.

Book Reviews

Medicinal Chemistry. Third edition. Edited by ALFRED BURGER, with 83 coauthors. Wiley-Interscience, New York, N. Y. 1970. Part I, xix + 835 pp; Part II, xv + 1390 pp. 26 × 18.7 cm. $75.00

The long-awaited third edition of Burger's "Medicinal Chemistry" (now in two volumes weighing 4.1 kg) will be welcomed by chemists and pharmacologists alike. The rate of expansion of medicinal chemistry is indicated by a comparison of the new edition with the second edition published just 10 years ago. This will show an increase of 50% in the number of pages of text, in a monumental collaborative effort involving the editor and 83 contributors. There are now 68 chapters, 6 of which were written by the editor.

The organization of the book has undergone a number of changes, and 13 new chapters have been added. The first volume presents the general background of medicinal chemistry. New chapters on "Drug Metabolism" and on "Stereochemistry and Biological Activity" provide concise and informative summaries of these increasingly important aspects of biological action. Other rapidly developing areas are represented by new sections on "Receptor Theories" and on the application of molecular orbital and computer calculations to medicinal chemistry. Drug design is discussed in a new chapter and the drug–host–parasite triangle is presented in a useful "Introduction to Chemotherapy," which sets the stage for a transition to the consideration of the general area of antiinfective and antiparasitic drugs. The greatly increased interest in semisynthetic penicillins and cephalosporins is reflected in a comprehensive chapter on β-lactam antibiotics, while the section on "Anthelmintics" serves to show the still almost entirely empirical approaches to the therapy of worm infections.

Part II covers vitamins and hormones in all their aspects. The need for effective nonsteroidal antiinflammatory agents is competently discussed in a new chapter on this topic, and the remainder of Part II is then given over to the systematic presentation of the drugs used in the treatment of functional disorders of all types. Increased interest in atherosclerosis is reflected in a new and comprehensive chapter on "Antilipemic Agents"; similarly, hypoglycemic drugs now have a section to themselves. An indication of recent developments in mental health is given by the expansion of the second edition's chapter on psychopharmacological agents (21 pp) into 4 separate sections on antipsychotics, antidepressants, antianxiety drugs, and hallucinogenic agents, with a total of 118 pages of text.

The subject index is detailed and comprehensive, and the addition of a cumulative author index is a new feature which will be welcomed by all readers. The literature has been covered up to 1968 in most cases, and Dr. Burger is to be congratulated on achieving both his aims: to bring the current state of knowledge in medicinal chemistry to the attention of interested workers, and to do so in a manner which permits the reader to appreciate both the successes achieved in the field and the many problems still unsolved.

The production and typography of the book are excellent, and it is remarkably free from errors. While the high price is to be regretted, it can be accounted for by reasons of increases in the cost of publication, coupled with the greatly increased size of the book itself.

UNIVERSITY OF CALIFORNIA
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J. CYMERMAN CRAIG

Biological Polyelectrolytes. Edited by ARTHUR VEIS. Marcel Dekker, New York, N. Y. 1970. viii + 291 pp. $19.75

Chemists think of cells and tissues as composed of a multitude of macromolecules. The structures of these huge molecules can be elucidated in part by studying their monomeric components and unions of these, up to limiting molecular weights beyond which chemical and physical methods available to us cannot yet be used. Even in the few cases where native macromolecules are fully understood, they may behave differently in the living environment as compared with *in vitro* conditions. This is due to the fact that polyfunctional and multicharged macromolecules are surrounded by other species with like features, as well as by solvent and other small molecules. It is in this biological orientation that the elements of "living" matter may some day be understood.

The five contributors to the present book have tried to start on a review of such studies. For example, they assess the intermolecular reactions of globular proteins (S. N. Timasheff) from their polyelectrolyte properties. Another chapter covers phase equilibria in systems of such interacting macromolecules (A. Veis); the thermodynamics of phase separations in random chain polymer mixtures; complex coacervation; demixing processes; and the biological implications of such data. These chapters, requiring a knowledge of kinetics, make a forceful contribution to our views of the cellular milieu.

The two remaining chapters, on nucleic acids and on the physical chemistry of polysaccharides, are more review than predictive. They help us to take another look at well-surveyed biochemical topics, but do not concern macromolecular *interactions* as much as the two broader topics mentioned above.

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ALFRED BURGER