New Organic Compounds for Insect Repellent Research

B. H. ALEXANDER, W. W. SULLIVAN[1], R. T. BROWN, and M. BEROZA
Entomology Research Division, Agricultural Research Service, U. S. Department of Agriculture, Beltsville, Md.

WIDESPREAD ACCEPTANCE of deet (*N,N*-diethyl-*m*-toluamide), a personal-use insect repellent (*4–7*) that is effective against a broad spectrum of biting arthropods (including the yellow fever and common malaria mosquitoes), led us to prepare compounds related to it. To find a better repellent, or possibly, one that might be superior against some of the insect species repelled by deet, we synthesized several hundred compounds for biological evaluation. This report outlines the preparation and physical constants of 32 compounds not previously recorded. Yields and elemental analyses are given in Tables I and II. These compounds have not been fully evaluated toxicologically and therefore none of the chemicals described in this paper are recommended at this time for personal use.

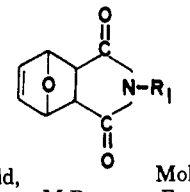
The amides were prepared by allowing the appropriate acid chloride to react with the amine or imine in benzene, and the carbamates were made by refluxing the sodium salt

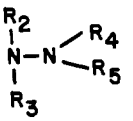
[1] Present address, Rohm and Haas Co., Philadelphia, Pa.

Table I. Amides, Sulfonamides, and Carbamates

No.	Compound	Yield, %	B.P./Mm.	n_D^{25} or M.P.	Molecular Formula	Elemental Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
1	3-Methyl-*N*-propyl-crotonamide	61	86–90/2.0	1.4823	$C_8H_{15}NO$	68.08	68.29	10.64	10.70	9.93	10.11
2	*m*-Methylbenzyl diethylcarbamate	78	108–117/0.5	1.4977	$C_{13}H_{19}NO_2$	70.55	70.94	8.65	8.54	6.33	6.71
3	2,2-Dimethyl-3-(2-methylpropenyl)-cyclopropane-methyl	61	100–110/0.5	1.4645	$C_{15}H_{27}NO_2$	71.10	71.93	10.74	10.87	...	...
4	Fenchyl diethyl-carbamate	50	92–6/0.4	1.4659	$C_{15}H_{27}NO_2$	71.10	71.39	10.74	10.49	...	...
5	2-Methyl-1-(*m*-toluoyl)-aziridine	59	140–146/14	1.5425	$C_{11}H_{13}NO$	75.40	76.00	7.99	8.19	...	...
6	*N*-Cyclohexyl-*N*-methyl-*m*-toluamide	73	126–142/0.1	1.5400	$C_{15}H_{21}NO$	77.92	77.62	9.09	8.58	...	...
7	1-Palmitoylpyrrolidine	79	200–205/1	1.4688	$C_{20}H_{39}NO$	...	...	...	...	4.53	4.58
8	1-Myristoylpyrrolidine	75	177–180/0.3	1.4699	$C_{18}H_{35}NO$	76.87	77.21	12.45	12.54	...	...
9	1-Octanoylpyrrolidine	83	110–115/0.3	1.4659	$C_{12}H_{23}NO$	...	...	...	...	7.62	7.90
10	1,1'-Adipoyldi-pyrrolidine	5	...	84–85	$C_{14}H_{24}N_2O_2$	66.67	66.01	9.52	9.33	11.12	10.56
11	1-Palmitoylhexamethyl-enimine	63	205/0.5	1.4727	$C_{22}H_{43}NO$	78.14	78.37	12.73	12.89	...	...
12	1,1'-Sebacoyldihexa-methylenimine	70	...	54–57	$C_{22}H_{40}N_2O_2$	72.13	71.83	10.93	10.94	7.65	7.92
13	1,1'-Azelaoydihexa-methylenimine	63	235/0.5	1.5090	$C_{21}H_{38}N_2O_2$	71.59	72.05	10.80	10.93	...	...
14	1,1'-Adipoyldihexa-methylenimine	38	220/0.5	1.5151	$C_{18}H_{32}N_2O_2$	...	...	...	...	8.48	9.12
15	1-Oleoylhexamethyl-enimine	77	225/1.5	1.4807	$C_{24}H_{45}NO$	...	...	...	...	3.83	3.84
16.	1-(*p*-Methoxyphenyl-sulfonyl)hexamethyl-enimine	83	...	60–62	$C_{13}H_{19}NO_3S$	57.99	57.38	7.06	7.28	...	...
17	1-(*p*-Ethoxyphenyl-sulfonyl)hexamethyl-enimine	78	...	75–78	$C_{14}H_{21}NO_3S$	59.36	59.47	7.42	7.45	...	...
17a	*N*-Butyl-*N*-methyl-*m*-toluamide	84	129–132/0.3	1.5165	$C_{13}H_{19}NO$	76.05	75.90	9.33	9.46	6.82	7.01[c]
b	*N*-Ethyl-*N*-propyl-*m*-toluamide	75	120–124/0.1	1.5189	$C_{13}H_{19}NO$	76.05	76.04	9.33	9.32	6.82	6.75
c	*N*-Ethyl-*N*-isobutyl-*m*-toluamide	73	124–129/0.6	1.5067	$C_{14}H_{21}NO$	76.66	76.86	9.65	9.70	6.39	6.46
d	*N*-Butyl-*N*-ethyl-*m*-toluamide	73	123–125/0.6	1.5099	$C_{14}H_{21}NO$	76.66	76.40	9.65	9.61	6.39	6.41

Table II. Oxabicycloheptenes and Hydrazo Compounds





No.	R	Yield, %	M.P.	Molecular Formula	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
18	$R_1 = -N=C(H)-(CH_2)_5CH_3$	94	61–4 decomp.	$C_{15}H_{20}N_2O_3$	65.19	65.19	7.30	6.71	10.14	10.34
19	$R_1 = -N=C$ (cyclohexylidene)	75	162–4 decomp.	$C_{14}H_{16}N_2O_3$	64.60	64.28	6.20	6.07	...	...
20	$R_1 = -N(H)-C_6H_5$	71	178 decomp.	$C_{14}H_{12}N_2O_3$	65.61	65.76	4.72	5.01	...	...
21	$R_1 = -N=C(H)-C_6H_4-o(-OCH_3)$	97	168–71 decomp.[a]	$C_{16}H_{14}N_2O_4$	64.42	64.12	4.73	4.63	...	...
22	$R_1 = -N=C(H)-C_6H_3-3,4(-OCH_2O-)$	94	153–4 decomp.[a]	$C_{16}H_{12}N_2O_5$	61.53	61.74	3.87	3.86	8.97	8.88
23	$R_1 = -N=C(H)$ (naphthyl)	89	158 decomp.[a]	$C_{19}H_{14}N_2O_3$	71.69	71.94	4.43	4.56	...	...
24	$R_2, R_4 = -C(=O)-C(H)-C(H)-C=C(CH_3)_2$ (cyclopropyl); $R_3, R_5 = H$	20	196–201 decomp.[a]	$C_{20}H_{32}N_2O_2$	72.24	71.84	9.70	9.82	...	...
25	$R_2, R_4 = -C(=O)-C_6H_4-o(-OC_2H_5)$; $R_3, R_5 = H$	51	211–212	$C_{18}H_{20}N_2O_4$	65.84	66.48	6.14	6.08	8.53	8.80
26	$R_2, R_3 = -C(=O)-C_6H_4-m(CH_3)$; $R_4, R_5 = -CH_3$	10	139–140	$C_{18}H_{20}N_2O_2$	72.95	73.22	6.80	6.89	9.45	9.96
27	$R_2, R_3 = -C(=O)-C_6H_4-m(CH_3)$; $R_4, R_5 = -C_2H_5$	39	100–102	$C_{20}H_{24}N_2O_2$	74.04	74.30	7.46	7.37	...	...
28	$R_2 = H$; $R_3 = -C(=O)-C_6H_4-m(CH_3)$; R_4 or $R_5 = =C(H)-C_6H_3-3,4(-OCH_2O-)$[b]	74	172–173 decomp.[a]	$C_{16}H_{14}N_2O_3$	68.07	68.27	9.92	9.91	5.00	5.46

[a] These compounds can exist as cis and trans isomers. [b] *m*-Toluic acid, piperonylidenehydrazide. [c] Compounds 17a–17d added after manuscript was accepted for publication.

of the alcohol with the *N,N*-dialkylcarbamoyl chloride in toluene by the usual procedures. The substituted Schiff's bases—for example, *N*-piperonylideneamino-7-oxabicyclo-[2.2.1]hept-5-ene-2,3-dicarboximide (compound 22)—were prepared by treating 7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (*2*) with hydrazine according to the general directions of Flett and Gardner (*3*) to give *N*-amino-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboximide. The appropriate aldehyde was then condensed (*1*) with the *N*-amino-oxabicyclo compound to give the desired substituted Schiff's base. *N*-anilino-7-oxabicyclo[2.2.1]-hept-5-ene-2,3-dicarboximide was prepared in good yield by allowing the afore-mentioned anhydride to react with phenylhydrazine (*3*).

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