and then a solution of acetic anhydride (20.7 g, 0.2033 mole) in $CHCl_3$ (25 ml) was added dropwise over 30 min. The suspension was heated to boiling and refluxed for 10 hr under N_2. Finally the mixture was cooled to room temperature, the suspended solid, consisting of unreacted N,N'-diphenylurea, was filtered off, and the $CHCl_3$ solution was washed several times with 1% $NaHCO_3$ solution and then with water, until neutral. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to give a residue consisting of a mixture of oil and solid product which was extracted several times with petroleum ether. A solid fraction was separated from the petroleum ether on standing, after filtration of the solid remaining in suspension. This solid fraction, filtered from the petroleum ether, was extracted with methanol; the insoluble portion consisting of N,N'-diphenylurea was removed, and the residue obtained by evaporation of the methanol solution was purified by chromatography on a Kieselgel G (Merck) column, using benzene-acetone (97:3) as eluent, giving an additional fraction of pure product. The product was further purified by crystallization from ethanol and gave colorless crystals (mp 81–82°).

Method D. 1-Geranylnormeperidine (VIII).—Normeperidine carbonate[9,10] (26.4 g) followed by geranyl bromide (21.7 g) was added to a sodium ethoxide solution prepared from sodium (2.3 g) and ethanol (230 ml). The mixture was stirred and refluxed for 1 hr under nitrogen, the solvent was evaporated under reduced pressure, and the residue was extracted with ether. The ethereal solution was treated with CO_2 to remove traces of unreacted normeperidine and filtered, and the ether was evaporated. The crude residue was then purified by chromatography on a Kieselgel G (Merck, 180 g) column, eluting with a 9:1 mixture of benzene and acetone to obtain the required product. A sample of the free base was distilled, bp 166–168° (0.1 mm), yielding a viscous oil. The pure hydrochloride, mp 143–144°, was obtained by treatment with HCl and subsequent crystallization from ethyl acetate.

(9) R. H. Thorp and E. Walton, *J. Chem. Soc.*, 559 (1948).

(10) J. Weijlard, P. D. Orahovats, A. P. Sullivan, Jr., G. Purdue, F. K. Heath, and K. Pfister, *J. Am. Chem. Soc.*, **78**, 2342 (1956), indicated that this material is the carbamate derived from 2 molecules of normeperidine.

Terpenes as Drugs. I. 1-Terpenyl-3-arylsulfonylureas

Gianfranco Pala, Antonio Mantegani, and Germano Coppi

Research Laboratories of Istituto de Angeli S.p.A., Milan, Italy

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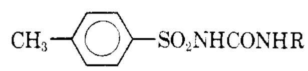
It is well known that in the hypoglycemic 1-alkyl-3-arylsulfonylureas the nature of the group in position 1 can be fairly widely varied without loss of activity;[1] compounds in which the above substituent was a cyclic terpene group have also been reported.[2] Our interest in the terpene field led us to synthesize three sulfonylureas of formula I, in which R is an acyclic terpene radical.



I

In order to draw a correlation of some significance, we have chosen a monoterpene radical (*i.e.*, geranyl), a partially saturated monoterpene radical (*i.e.*, citronellyl), and a sesquiterpene radical (*i.e.*, farnesyl), keeping the aryl component unchanged. Hypoglycemic tests have shown that only 1-citronellyl-3-*p*-tolylsulfonylurea is active, even though its action was found to be rather fleeting. As the citronellyl radical is more similar, than the other two, to a saturated alkyl group, the conclusion may be drawn that in hypoglycemic arylsulfonylureas the introduction of a markedly terpene-type radical in position 1 leads to inactive products.

(1) K. Gerzon, E. V. Krumkalns, R. L. Brindle, F. J. Marshall, and M. A. Root, *J. Med. Chem.*, **6**, 760 (1963).

(2) J. A. Aeschlimann and A. Stempel, U. S. Patent 2,928,871 (1960).

Experimental Section

1-Citronellyl-3-*p*-tolylsulfonylurea.—A solution of citronellylamine[3] (6 g, 0.368 mole) and ethyl N-(*p*-tolylsulfonyl)carbamate (10.6 g, 0.435 mole) in anhydrous toluene (120 ml) was refluxed for 5 hr. The solvent was removed *in vacuo*, and the residue was repeatedly washed with formamide and then extracted with ether; after washing with water, the ethereal solution was dried (Na_2SO_4). The solvent was then evaporated to give a viscous oil (9.8 g, 72% yield).

Anal. Calcd for $C_{18}H_{28}N_2O_3S$: C, 61.33; H, 8.00; N, 7.95; S, 9.09. Found: C, 61.48; H, 8.08; N, 7.82; S, 9.01.

1-Geranyl-3-*p*-tolylsulfonylurea.—A solution of geranylamine[4] (3 g, 0.0196 mole) and ethyl N-(*p*-tolylsulfonyl)carbamate (5.3 g, 0.0219 mole) in anhydrous toluene (60 ml) was refluxed as above. The solvent was removed and the residue was triturated with ether to give a colorless solid (5.7 g, 82% yield). An analytical sample, obtained by recrystallization from ethanol, melted at 89–90° (uncor).

Anal. Calcd for $C_{18}H_{26}N_2O_3S$: C, 61.68; H, 7.48; N, 7.99; S, 9.14. Found: C, 61.71; H, 7.50; N, 8.04; S, 9.12.

1-Farnesyl-3-*p*-tolylsulfonylurea.—A solution of farnesylamine[5] (6.5 g, 0.0294 mole) and ethyl N-(*p*-tolylsulfonyl)carbamate (8 g, 0.0328 mole) in anhydrous toluene (100 ml) was refluxed as above and worked up. The product was obtained as a viscous oil (8.6 g, 70% yield).

Anal. Calcd for $C_{23}H_{36}N_2O_3S$: C, 65.99; H, 8.19; N, 6.69; S, 7.66. Found: C, 65.83; H, 8.23; N, 6.70; S, 7.54.

(3) D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **37**, 881 (1954).

(4) M. S. Kharasch, W. Nudenberg, and E. K. Fields, *J. Am. Chem. Soc.*, **66**, 1276 (1944).

(5) Hoffmann-La Roche & Co., A.-G., Belgian Patent, 617,175 (1962).

Potential Antimalarial Substances. Amides of *o*-Ethoxy- and *p*-Isopropylbenzoic Acids[1]

Leslie M. Werbel, Carolyn A. Hess, and Edward F. Elslager

Research Laboratories, Parke, Davis and Company, Ann Arbor, Michigan

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Preliminary antimalarial screening results suggested that the dicyclohexylamide of *o*-ethoxybenzoic acid (**8**) (Table I) and the diethylamide of *p*-isopropylbenzoic acid (**9**) (Table II) had some activity against *Plasmodium berghei* in mice.[2] Therefore, authentic samples of **8** and **9** were synthesized together with several analogs (Tables I and II). None of the amides described herein was active against *P. berghei* in the mouse when administered in a single subcutaneous dose of 640 mg/kg.[2]

Experimental Section[3]

Acid Chlorides.—The acid (0.12 mole) and 50 ml of $SOCl_2$ were heated for 5 hr on a steam bath. The mixture was cooled to room temperature and the excess $SOCl_2$ was removed *in vacuo* yielding the crude acid chloride as a liquid.

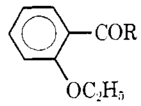
Amides.—To a cooled solution of 0.15 mole of the crude acid chloride in 150 ml of benzene, 0.3 mole of the amine was added. After the addition of amine, an additional 50 ml of benzene was added and the mixture was allowed to warm to room temperature. The mixture was stirred overnight and the solid which formed was removed by filtration. The solid was triturated with water to remove amine hydrochloride, and any residual material was removed by filtration and recrystallized. The benzene

(1) This investigation was supported by U. S. Army Medical Research and Development Command Contract DA-49-193-MD-2754.

(2) The antimalarial screening was carried out by Dr. Leo Rane of the University of Miami, and test results were supplied through the courtesy of Dr. David P. Jacobus of the Walter Reed Army Institute of Research.

(3) Melting points (corrected) were taken in open capillary tubes in a Thomas-Hoover capillary melting point apparatus.

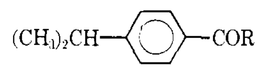
TABLE I
AMIDES OF *o*-ETHOXYBENZOIC ACID



No.	R	Mp or bp (mm), °C	Yield purified, %	Purification solvent[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
1	NH-3-$C_5H_4N^b$	66–68	33	A	$C_{14}H_{14}N_2O_2$	69.40	69.84	5.82	6.12	11.57	11.60
2	NHC_6H_5	70–71	50	A	$C_{15}H_{15}NO_2$	74.66	74.58	6.27	6.29	5.81	5.46
3	$N(C_2H_5)C_6H_5$	112–114 (0.2)	49	. .	$C_{17}H_{19}NO_2$	75.81	75.73	7.11	7.28	5.20	5.15
4	$NH(CH_2)_2C_6H_5$	56–58	28	A	$C_{17}H_{19}NO_2$	75.81	76.09	7.11	7.25	5.20	5.09
5	$NHCH_2C_6H_4$-*p*-CH_3O	54–56	50	B	$C_{17}H_{19}NO_3$	71.59	71.60	7.07	6.69	4.92	4.80
6	$N(C_2H_5)CH_2C_6H_5$	133–135 (0.1)	33	. .	$C_{18}H_{21}NO_2$	76.29	76.33	7.47	7.48	4.94	4.91
7	$N(C_6H_5)_2$	97–99	78	A	$C_{21}H_{19}NO_2$	79.47	79.79	6.03	6.09	4.42	4.49
8	$N(C_6H_{11})_2^c$	170–172 (0.3)	32	. .	$C_{21}H_{31}NO_2$	76.55	76.46	9.49	9.54	4.25	4.17

[a] A, isooctane; B, ethanol–water. [b] C_5H_4N represents the pyridyl radical. [c] C_6H_{11} represents the cyclohexyl radical.

TABLE II
AMIDES OF *p*-ISOPROPYLBENZOIC ACID



No.	R	Mp or bp (mm), °C	Yield purified, %	Purification solvent[a]	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found
9	$N(C_2H_5)_2^d$	97–100 (0.4)	25	. .	$C_{14}H_{21}NO$	76.66	76.41	9.65	9.72	6.38	6.21
10	NH-3-$C_5H_4N^b$	100–101	14	A	$C_{15}H_{16}N_2O$	74.97	75.12	6.71	6.77	11.66	11.47
11	$N(CH_2)_5$	60–61	37	A	$C_{15}H_{21}NO$	77.89	77.87	9.15	9.36	6.06	6.12
12	NHC_6H_5	129–131	43	B	$C_{16}H_{17}NO$	80.30	80.04	7.16	7.19	5.85	5.96
13	$N(CH_3)(C_6H_{11})^c$	80–81	38	A	$C_{17}H_{25}NO$	78.71	78.98	9.72	9.95	5.40	5.35
14	$N(C_2H_5)(C_6H_5)$	124–127 (0.2)	36	. .	$C_{18}H_{21}NO$	80.86	80.64	7.92	7.87	5.24	5.17
15	$NH(CH_2)_2C_6H_5$	110–112	19	B	$C_{18}H_{21}NO$	80.86	80.59	7.92	7.90	5.24	5.26
16	$NHCH_2C_6H_4$-*p*-MeO	119–121	33	B	$C_{18}H_{21}NO_2$	76.29	76.08	7.47	7.43	4.94	4.82
17	$N(C_2H_5)CH_2C_6H_5$	168–169 (0.4)	12	. .	$C_{19}H_{23}NO$	81.10	80.99	8.24	8.49	4.98	4.81
18	$N(C_6H_{11})_2^c$	170–172 (0.1)	43	. .	$C_{22}H_{31}NO$	81.18	80.19	9.60	9.68	4.30	4.19

[a–c] See corresponding footnotes, Table I. [d] W. F. Barthel, J. Leon, and S. A. Hall, *J. Org. Chem.*, **19**, 485 (1954).

from the original filtrate was removed *in vacuo* and the residue was recrystallized or distilled.

Acknowledgment.—The authors wish to thank Mr. Charles E. Childs and his staff for the microanalytical data reported herein.

4-(1-Methyl-4-pyrrolidinobutylamino)-7-chloroquinoline and 4-(1-Methyl-4-morpholinobutylamino)-7-chloroquinoline as Potential Antimalarials

PETER K. IBER AND BETTY J. BOONE

Division of Biochemistry, Walter Reed Army Institute of Research, Washington, D. C. 20012

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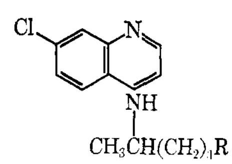
Increased interest in finding a prophylactic agent against drug-resistant *Plasmodium falciparum* and *Plasmodium vivax* has led to the synthesis of two new substituted quinolines, 4-(1-methyl-4-pyrrolidinobutylamino)-7-chloroquinoline (I) and 4-(1-methyl-4-morpholinobutylamino)-7-chloroquinoline (II) (Table I). 4-(1-Methyl-4-bromobutylamino)-7-chloroquinoline (III),[1] upon reaction with morpholine or pyrrolidine, gave I and II, respectively. Preliminary reports[2] show these compounds to be active against *Plasmodium berghei* infected mice.

TABLE I
ANTIMALARIAL TEST DATA

Compd	No. of mice[a]	Dose, mg/kg	Mean survival time, days[b]	Deaths
I	5	40	15.2	5
II	5	80	13.8	4
II	5	160	14.4	4

[a] Mice infected with *P. berghei*. [b] Treatment is withheld for 3 days after infection. Death occurs in untreated controls within 6–8 days.



I, R = pyrrolidino
II, R = morpholino

Experimental Section[3]

4-(1-Methyl-4-pyrrolidinobutylamino)-7-chloroquinoline (I).—4-(1-Methyl-4-bromobutylamino)-7-chloroquinoline (III)[1] (13.2

(1) M. Carmack, H. Bullitt, Jr., G. Handrick, L. W. Kissinger, and I. Von, *J. Am. Chem. Soc.*, **68**, 1220 (1946).

(2) We wish to thank Dr. Leo Rane, University of Miami, Miami, Fla., for the preliminary test data.

(3) Melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus. The microanalyses were performed by Mr. Joseph Alicino, Metuchen, N. J. 08840.