2,4-Dicarbamyl-3-oxapentane from 2,4-Dicarbethoxy-3-oxapentane (II to III). In a 35-ml. bomb, 1.009 grams (0.005 mole) of *dl* or meso diethyl dilactate and 15 ml. of liquid ammonia were heated at 150° C. for 10 hours. The bomb was cooled to −20° C. and opened, and the excess ammonia allowed to escape. The crude diamide was then taken up in 10 ml. of boiling absolute ethanol, treated with charcoal, and filtered. The analytical samples were recrystallized three more times from acetone. The yield of *dl*-lactic acid diamide was 600 mg. (75%) of needles which melted at 182–83° C. The literature gives a melting point of 184° C. (*7*). Analysis. Calculated for $C_6H_{12}N_2O_3$: C, 44.99; H, 7.55 N, 17.49. Found: C, 45.08; H 7.95; N, 17.53. Mesolactic acid diamide: yield 550 mg. (69%) of plates which melted at 133-35° C. The literature gives a melting point of 136° C. (*7*). Analysis. Calculated for $C_6H_{12}N_2O_4$: C, 44.99; H, 7.55; N, 17.49. Found: C, 44.76; H, 7.84; N, 17.83.

Preparation of 2,4-Dimethyl-3-oxapentane-1,5-diol from 2,4-Dicarbethoxy-3-oxapentane (IV from II). The procedure was essentially that used by Sexton and Britton, except that the scale was one tenth (*5*). The reduction products were identical (by infrared) with the materials obtained from VII to the acetate (VI), and then to the glycol (IV). The course of the reduction was followed by gas chromatography using a Carbowax 20M column at 191° C.

Preparation of Bis-*p*-nitrobenzoate Esters of 2,4-Dimethyl-3-oxapentane-1,5-diol (IV to V). The *dl* or meso glycols (IV) were esterified by heating a mixture of the appropriate glycol (0.670 gram, 0.005 mole) and *p*-nitrobenzoyl chloride (1.856 grams, 0.01 mole) to 100° C. for 15 minutes with HCl evolution. After this, the reaction mixture was flushed with dry nitrogen and cooled. The crude esters were recrystallized from ethanol four times and dried at 1-torr vacuum at room temperature for 10 hours. The *dl*-ester yield was 2.0 grams (81%) with a melting point of 141-42° C. The literature melting point was 142–43° C. (*5*). Analysis. Calculated for $C_{20}H_{20}N_2O_8$: C, 55.55; H, 4.66; N, 6.48. Found: C, 55.57; H, 4.59; N, 6.34. The meso ester yield was 1.85 grams (75%) with a melting point of 115-16° C. Analysis. Calculated for $C_{20}H_{20}N_2O_9$: C, 55.55; H, 4.66; N, 6.48. Found: C, 55.47; H, 4.61; N, 6.63.

1,5-Diacetoxy-2,4-dimethyl-3-oxapentane (VI). In a 1.2-liter autoclave were placed 292.8 grams (1.7 moles) of bis(2-chloroisopropyl) ether, 400 grams of anhydrous potassium acetate, and 300 ml. of acetic acid. Before the autoclave was closed, the reaction mixture was stirred. The mixture was heated to 130° C. for 10 hours. The cold reaction mixture was dissolved in 2 liters of water and extracted three times with 200-ml. portions of diethyl ether. The combined extracts were washed with 100 ml. of water and dried over anhydrous sodium sulfate. The ether was removed with a rotary evaporator and a water bath (40° to 50° C.). The resultant diacetate was fractionated through a 20 × 1 cm. distillation column with metal packing to yield 150 grams (40.5%) at 118–19° C. at 9 mm. (sp. g. 25/25 1.041 n_D^{20} 1.4235). Analysis. Calculated for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31. Found: C, 54.98; H, 8.40

Preparation of 1,5-Dihydroxy-2,4-dimethyl-3-oxapentane (IV). A mixture of 130 grams of 1,5-diacetoxy-2,4-dimethyl-3-oxapentane (0.596 mole), 100 ml. of absolute methanol, and one drop of concentrated sulfuric acid was refluxed for 10 hours and made basic with a concentrated solution of sodium hydroxide. Methanol was removed under reduced pressure to leave a residue of 89 grams of the crude glycol. Distillation with a Wheeler spinning band column of the crude product at 84° C. and 0.1 mm. gave 85 grams (91.4%) of IV. The separation of 10.0 grams of the mixture of the *dl* and meso forms of IV by preparative gas chromatography gave 3.2 grams of the *dl* glycol (IV) and 3.4 grams of the meso glycol (IV) (*dl* glycol n_D^{25} 1.4426. Analysis. Calculated for $C_6H_{14}O_4$: C, 53.71; H, 10.52. Found: C, 53.52; H, 9.90 meso glycol n_D^{25} 1.4356. Analysis. Calculated for $C_6H_{14}O_4$: C, 53.71; H, 10.52. Found: C, 53.46; H, 10.61. Literature n_D^{25} 1.440, b.p. 102° C. at 5 mm. (*5*).

The ditrifluoroacetates were prepared and carefully examined by F^{19} NMR spectroscopy for the presence of any secondary esters, none being observed in either the *dl* or meso glycols of IV. The chemical shifts of the fluorinated secondary diesters and the primary diesters are 75.82 ± 0.02 and 75.55 ± 0.02 p.p.m., respectively, relative to trichlorofluoromethane (*1*).

LITERATURE CITED

(1) Ingham, J.D., Lawson, D.D., Manatt, S.L., Rapp, N.S., Hardy, J.P., *J. Macromol. Chem.* **1**, 75 (1965).
(2) Lawson, D.D., Getz, H.R., *Chem. Ind.* **1961**, 1404.
(3) Lawson, D.D., Havlik, A.J., *J. Gas Chromatog.* **1** (5), 17–20 (1963).
(4) Littlewood, A.B., Phillips, C.S.C., Price, D.T., *J. Chem. Soc.* **1955**, 1483.
(5) Sexton, A.R., Britton, E.C., *J. Am. Chem. Soc.* **75**, 4357 (1953).
(6) Summerbell, R.K., Jerina, D.M., Grula, R.J., *J. Org. Chem.* **27**, 4433-6 (1962).
(7) Vieles, P., *Ann Chim.* **3** (11), 143 (1935); and references to earlier papers.

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Derivatives of Anthranilic Acid

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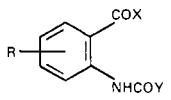
The preparation of carbamates and ureas derived from anthranilic acid, its methyl ester, and substituted anthranilic acids is described. A summary of the activity of these compounds in two anti-inflammatory screening assays is also presented.

CARBAMATES and ureas derived from anthranilic acid, its methyl ester, and substituted anthranilic acids were prepared because of their similarity to compounds with anti-inflammatory activity (*5, 6, 10, 11, 12*). The compounds prepared (Ia-x) together with appropriate analytical and physical data are listed in Table I. Ia-x were prepared by the procedures outlined in the experimental section.

In the preparation of Ia, d, and e, a second compound was formed. Infrared spectra and elemental analyses showed that these compounds were *N*-(*o*-alkoxycarbonylaminobenzoyl) anthranilic acids (IIa-c). The infrared spectra of IIa-c had a triplet in the carbonyl region—the most intense

[1] Deceased.

Table I. Derivatives of Anthranilic Acid



Compound No.	R	X	Y	m.p., °C.[a]	Yield, %	Solvent[b]
Ia	H	OH	OC_2H_5	126–128[c]	50	1
b	H	OH	O-i-C_3H_7	182–184[d]	60	2–3
c	H	OH	$OCH_2CH=CH_2$	125–127	75	4–3
d	H	OH	O-*n*-C_4H_9	95–97	25	5–6
e	H	OH	O-i-C_4H_9	113–115	29	5–6
f	H	OH	$OCH_2CH(C_2H_5)_2$	110–111	82	7–3
g	H	OH	$OCH_2CH(CH_2)_3CH_3$ | C_2H_5	60–62	46	8
h	H	OH	OC_6H_5	153–154	68	7–3
i	H	OH	$OCH_2C_6H_4$-*p*-NO_2	196–198	64	9
j	3-CH_3	OH	OC_2H_5	132–134	34	1
k	4-CH_3	OH	OC_2H_5	158–159	63	1
l	5-CH_3	OH	OC_2H_5	154–156	66	1
m	6-CH_3	NH_2	OC_2H_5	180–182	5	9
n	5-CF_3	OH	OC_2H_5	218–219	57	9–5
o	4,5 	OH	OC_2H_5	213–214	58	10–3
p	H	OCH_3	NH-C_6H_4-*m*-CH_3	136–137	65	4–6
q	H	OCH_3	NH-C_6H_4-*o*-CH_3	204–206	65	5–6
r	H	OCH_3	NH-C_6H_4-*p*-OCH_3	159–161	54	5–6
s	H	OCH_3	NH-C_6H_4-*p*-Cl	185–186	59	5–6
t	H	OCH_3	NH-C_6H_4-*m*-Cl	161–162	53	4–6
u	H	OCH_3	NH-C_6H_4-*o*-Cl	185–186	68	5–6
v	H	OCH_3	NH-C_6H_4-*p*-NO_2	372–374[e]	62	11–12–6
w	H	OCH_3	NH-C_6H_4-*m*-NO_2	352–354[e]	49	11–12–6
x	H	OCH_3	NH-C_6H_4-*p*-NH_2	174–175[f]	40	5–6

[a] Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are corrected unless otherwise specified. [b] Solvents used for recrystallizations: 1, carbon tetrachloride; 2, 2-propanol; 3, water; 4, acetone; 5, chloroform; 6, petroleum ether (b.p. 30–60° C.); 7, methanol; 8, hexane; 9, ethyl acetate; 10, ethanol; 11, pyridine; 12, ether. [c] Literature (2) m.p. 123–125° C. (H_2O). [d] Reported (7) m.p. 149–150° C. but no evidence was given to show that this compound has the structure cited. [e] Taken in a metal block and is uncorrected. [f] Melts with decomposition to a cloudy melt.

peak was at 5.8 to 5.82 microns (carbamate) while the two smaller peaks were at 5.91 microns (acid) and 6.01 microns (amide). The peak at 5.91 microns sometimes appeared as a shoulder on the 5.8 to 5.82 microns peak. By comparison, the carbamates had two peaks of equal intensity at about 5.75 microns (carbamate) and 5.95 microns (acid). IIa-c were probably formed by the reaction of anthranilic acid with the mixed anhydrides of Ia, d, and e. Ix was obtained by catalytic hydrogenation of Iv in acetic acid. If the reduction was performed in dimethylformamide or if the acetic acid was neutralized so that Ix was allowed to stand in a basic solution, a quinazolinedione was formed.

The compounds, Ia-x, were tested for anti-inflammatory activity using the ultraviolet erythema assay (*9*) and the carrageenin-filter paper granuloma assay (*4, 8*) in adrenalectomized rats. The compounds were inactive in the erythema assay and, although several of the compounds were active in the granuloma assay after subcutaneous administration, none was effective after oral administration (*1*).

EXPERIMENTAL

Isatoic Acid *N*-alkyl and Aryl Esters (Anthranilic Acid Carbamates) (Ia-o). Equivalent amounts of anthranilic acid and triethylamine in chloroform (100 ml. per 0.1 mole) were stirred and cooled, while an equivalent amount of the appropriate chlorocarbonate dissolved in chloroform was added dropwise. The rate of addition was adjusted so that the temperature did not exceed 10° C. Stirring was continued for several hours at room temperature, and the solution was left overnight. The solution was concentrated and the concentrate diluted with petroleum ether. The resulting solid was filtered, suspended in water, refiltered, washed with water, dried, and recrystallized.

Methyl *N*-Substituted carbamoylanthranilates (Ureas of Methyl Anthranilate) (Ip-x). To a stirred solution of 15.1 grams (0.1 mole) of methyl anthranilate in 200 ml. of dry benzene or hexane was added 0.1 mole of the appropriate, commercially available isocyanate, followed in five minutes by 10 drops of triethylamine. The mixture was stirred overnight at room temperature and filtered. The solid was washed with benzene and benzene–petroleum ether, dried, powdered, and recrystallized.

***N*-(o-Alkoxycarbonylaminobenzoyl) Anthranilic Acids (IIa-c).** Crude Ia, d, and e were recrystallized from methanol containing a little water. The first crop of solid in each case was the corresponding benzoyl derivative of anthranilic acid. Dilution of the filtrates with water gave the carbamates. The benzoyl derivatives were purified by recrystallization.

Anal. Calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.54; H, 5.29; N, 8.64. Equivalent weight, 328. Found, 331, 330, 328. IIa, m.p. 236–238° C. (ethanol-water).

Anal. Calcd. for $C_{19}H_{20}N_2O_5$: C, 64.03; H, 5.66; N, 7.86. Found: C, 63.89; H, 5.63; N, 7,81. IIb, m.p. 169–171° C. (methanol).

Anal. Calcd. for $C_{19}H_{20}N_2O_5$: C, 64.03; H, 5.66; N, 7,86. Found: C, 64.02; H, 5.56; N, 7.89. IIc, m.p. 208–209° C. (methanol).

6-Methylanthranilamide. A mixture of 5.2 grams (0.04 mole) of 2-cyano-*m*-toluidine (*3*) and 35 ml. of 50% aqueous sulfuric acid was stirred under reflux for 5 hours. The solution was cooled and made alkaline with 40% sodium hydroxide. The resulting solid was filtered to give 1 gram of recovered starting material. The filtrate was neutralized with acetic acid and extracted first with chloroform and then with 1-butanol. The extracts were washed with water, dried (sodium sulfate), and evaporated separately. The residues were combined and recrystallized from chloroform. Yield 1.5 grams (31%), m.p. 138–139° C.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.98; H, 6.71; N, 18.66. Found: C, 63.58; H, 7.04; N, 18.59.

Methyl *N*-(*p*-Aminophenylcarbamoyl) Anthranilate (Ix). A mixture of 6.3 grams (0.02 mole) of Iv, 0.5 gram of 10% palladium on carbon, and 250 ml. of acetic acid was hydrogenated on a Parr apparatus under 3 atm. of hydrogen. The catalyst was filtered, and the filtrate was added to a stirred mixture of ice water and chloroform. To this mixture was added slowly 10% sodium hydroxide until the solution was neutral. The layers were separated, and the aqueous layer was extracted three times with chloroform. The combined chloroform layers were washed with water until neutral, dried, and evaporated in vacuo at room temperature. The residue was recrystallized.

If dimethylformamide was used in place of acetic acid in the hydrogenation and the filtered reaction solution was diluted with water, the resulting solid was the cyclized 3-(*p*-aminophenyl) quinazoline-2,4-dione, m.p. 335–337° C. (uncorrected) (pyridine-ether).

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 66.14; H, 4.72; N, 16.53. Found: C, 65.98; H, 4.59; N, 16.32.

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LITERATURE CITED

(1) Birnie, J. H., Smith Kline and French Laboratories, unpublished data, 1964–1965.
(2) Cohen, E., Klarberg, B., *J. Am. Chem. Soc.* **84**, 1994 (1962).
(3) Gabriel, S., Thieme, A., *Ber.* **52**, 1079 (1919).
(4) Meier, R., Schuler, W., Desaulles, P., *Experentia* **6**, 469 (1950).
(5) Scherrer, R.A., Winder, C.V., Short, F.W., Abstracts of the 9th Medicinal Chemistry Symposium of the American Chemical Society, Minneapolis, Minnesota, p. 11a, June 1964.
(6) Scherrer, R.A., "Annual Reports in Medicinal Chemistry," C. Cain, Ed., p. 224, Academic Press, New York, 1966.
(7) Staiger, R.P., Miller, E.B., *J. Org. Chem.* **24**, 1214 (1959).
(8) Tanaka, A., Kobayaski, F., Miyake, T., *Endocrinol. Japon.* **7**, 357 (1960).
(9) Winder, C.V., Wax, J., Burr, V., Benn, M., Rosiere, C.E., *Arch. Intern. Pharmacodyn.* **116**, 261 (1958).
(10) Winder, C.V., Wax, J., Scotti, L., Scherrer, R.A., Jones, E.M., Short, F.W., *J. Pharmacol. Exptl. Therap.* **138**, 405 (1962).
(11) Winder, C.V., Wax, J., Serrano, B., Jones, E.M., McPhee, M.L., *Arthritis Rheum.* **6**, 36 (1963).
(12) Winder, C.V., Wax, J., Welford, M., *J. Pharmacol. Exptl. Therap.* **148**, 422 (1965).

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Thermal Isomerization of Methyl Abietate

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Methyl abietate has been found to isomerize at 200° C. at about the same rate as the free acid. The same final equilibrium distribution of palustrate (14%), neoabietate (5%), and abietate (81%) was obtained as observed for the free acid. Disproportionation, however, was extensive in the case of the ester in contrast to the free acid. The addition of base to the ester very strongly inhibited isomerization and prevented disproportionation.

IN A PREVIOUS investigation concerning the isomerization of the four conjugated dienoic resin acids, the authors reported for the first time that abietic acid at 200° C. was isomerized to a final equilibrium mixture of 14% palustric, 5% neoabietic acid, and 81% abietic acid (*7*). The same final distribution of acids was also noted for the first time when levopimaric, palustric, and neoabietic acids were treated in the same fashion. Disproportionation under these conditions was found to be negligible.

The methyl esters of levopimaric (*4*), palustric (*3*), and neoabietic (*5*) acids have been found to isomerize to methyl abietate very slowly as compared with the acids. No report has been made in the literature concerning the reverse isomerization of methyl abietate to methyl palustrate, neoabietate, and levopimarate. It was, therefore, decided to investigate this problem.

Methyl abietate was sealed in borosilicate glass tubes under nitrogen and heated in a bath at 200° C. The tubes were removed at intervals and analyzed by means of GLPC (*2*), optical rotation, and ultraviolet absorption spectrum. The results are summarized in Tables I and II. Three interesting observations were made. First, methyl abietate isomerizes at 200° C. to give the same final equilibrium ratio of abietate (81%), palustrate (14%), and neoabietate (5%) as the free acid (Table I). Second, the ester isomerizes at essentially the same rate as the free acid. Third, the ester undergoes rather extensive disproportionation (Table II) as compared with the free acid which does not disproportionate under these conditions.

The isomerization of methyl abietate was repeated at 180° C. and the same ratio of abietate, palustrate, and neoabietate was obtained. Disproportionation also occurred at the lower temperature, but at a slower rate. The isomerization followed first order kinetics with respect to the loss of methyl abietate for the first 50 minutes; $k = 3.67 \times 10^{-5}$ sec.$^{-1}$ at 180° C.; $t_{1/2} = 5.3$ hours. These values are essentially the same as those reported (*7*) for the isomerization of the free acid at 180° C.

In the work on the free acid (*7*), it was shown that the addition of a small amount of base strongly inhibited the isomerization. Consequently, the addition of a 5 mole

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