[CONTRIBUTION FROM THE RICHARDSON CHEMICAL LABORATORY OF TULANE UNIVERSITY]

THE SYNTHESIS AND ANTI-TUBERCULAR EVALUATION OF SOME AMIDES OF 10-HENDECENOIC AND *p*-NITRO-BENZENESULFONIC ACIDS

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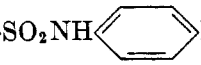
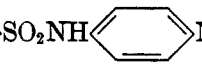
As a part of a broad program of evaluation of certain organic types as anti-tubercular chemotherapeutic agents, we have prepared a series of amides of *p*-nitrobenzenesulfonic and 10-hendecenoic acids. The amides of *p*-nitrobenzenesulfonic acid were largely of two types,

(a) O_2N  SO_2NH  $NHCOAr$

and (b) O_2N  SO_2NH  $NHO_2SAr.$

Two possible routes (A and B) to these types were tried, and the methods used are shown in the accompanying diagram. Route B was chosen as better for the synthesis of II and related types since 4-(*p*-nitrobenzenesulfonamido)aniline (I) could be synthesized in large quantity and the last step merely involved reaction with the various acid chlorides (ArCOCl or $ArSO_2Cl$) used. In route A reaction with the acid chlorides occurred in the first step, requiring each compound prepared to be carried through the several steps shown to reach II. The amides (II) prepared are shown in Table I.

A number of new amides of 10-hendecenoic acid were prepared by reaction of amines with 10-hendecenoyl chloride. These are shown in Table II. The *in vitro* effectiveness of several 10-hendecenamides in growth inhibition studies has been reported by Brodersen and Kjaer (1) but these workers did not include *M. tuberculosis* in the several microorganisms used. In addition to the amides listed in Table II, the amides of *o*- and *p*-aminobenzoic acids, previously prepared by Broderson and Kjaer (1), were prepared and tested for *in vitro* anti-tubercular activity.

In the *in vitro* testing[3] of the compounds listed in this paper against the H37Rv strain of *M. tuberculosis* in aqueous medium, those given below were found to be effective in inhibiting the growth of the organism at a concentration level of 0.002 mg. of drug per 10 ml. of test medium or lower: 1-(*p*-nitrobenzenesulfonamido)-4-(3′,5′-dinitrobenzamido)benzene (Table I, No. 5); *p*,*p*′-bis-(10-hendecenamido)diphenyl sulfone (Table II, No. 2); and *p*-(10-hendecenamido)sali-

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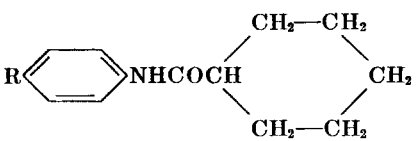
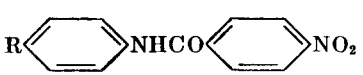
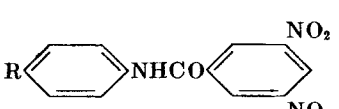
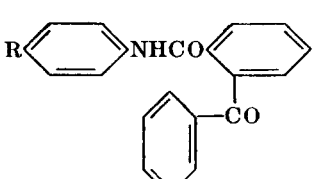
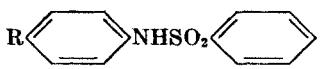
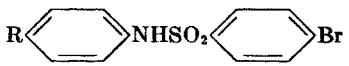
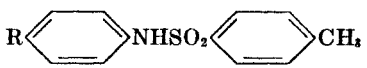
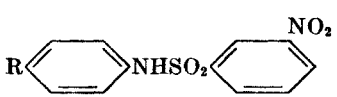
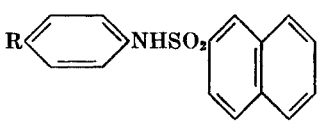
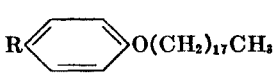
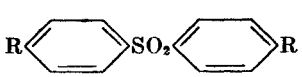
[3] The biological tests were carried out in the laboratories of the Eli Lilly and Co. of Indianapolis, Ind. We are grateful to Dr. Reuben G. Jones and Mr. F. G. Jones for arranging the tests.

TABLE I

AMIDES OF *p*-NITROBENZENESULFONIC ACID

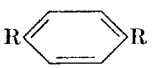
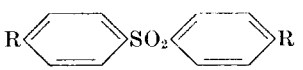
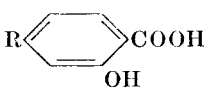
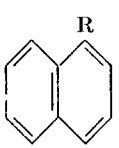
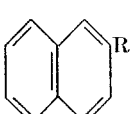
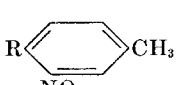
No.	COMPOUND[a]	PROCEDURE	M.P., °C.	YIELD, %	MOLECULAR FORMULA	N ANALYSES	
						Calc'd	Found
1		B	183–184	74	$C_{30}H_{45}N_3O_5S$	7.50	7.48
2		B	259–260	58	$C_{19}H_{21}N_3O_5S$	10.42	10.38
3		B	278–279	69	$C_{19}H_{15}N_3O_5S$	10.61	10.67
4		B	269–270	65	$C_{19}H_{14}N_4O_7S$	12.67	12.70
5		B	268–269	60	$C_{19}H_{13}N_5O_9S$	14.38	14.65
6		B	243–244	59	$C_{26}H_{19}N_3O_6S$	8.39	8.36

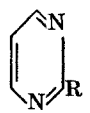
7		B	238–239	74	$C_{18}H_{15}N_3O_6S_2$	9.70	10.00
8		B	304–306	55	$C_{18}H_{14}BrN_3O_6S_2$	8.20	8.30
9		B	273–274	65	$C_{19}H_{17}N_3O_6S_2$	9.37	9.38
10		B	237	50	$C_{18}H_{14}N_4O_8S_2$	11.72	11.82
11		B	249	85	$C_{22}H_{17}N_3O_6S_2$	8.70	9.00
12		A	135–136	66	$C_{30}H_{46}N_2O_5S$	5.86[b]	5.80[b]
13		A	278–280	78	$C_{24}H_{18}N_4O_{10}S_3$	8.77	8.98

[a] R = *p*-$NO_2C_6H_4SO_2NH$—. [b] Analysis for sulfur.

TABLE II

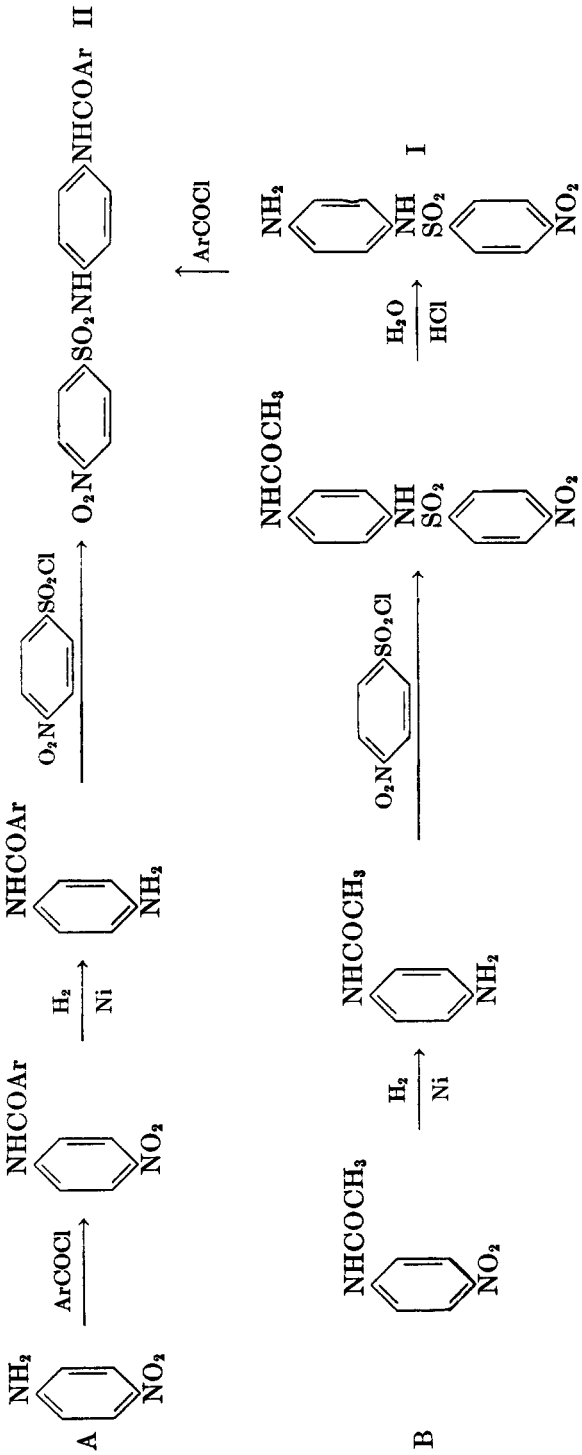
AMIDES OF 10-HENDECENOIC ACID

No.	COMPOUND[b]	PROCEDURE	M.P., °C.	YIELD, %	MOLECULAR FORMULA	N ANALYSES	
						Calc'd	Found
1		B	191.5–192.5	73	$C_{25}H_{44}N_2O_2$	6.36	6.36
2		B	131.5–132.0	58[a]	$C_{34}H_{48}N_2O_4S$	4.83	5.23
3		C	179–180	27	$C_{18}H_{25}NO_4$	4.38	4.29
4		C	101	23	$C_{21}H_{27}NO$	4.53	4.61
5		B	92.5	40	$C_{21}H_{27}NO$	4.53	4.68
6		B	48–49	47	$C_{18}H_{26}N_2O_3$	8.80	8.71
7		C	79	15	$C_{16}H_{24}N_2O$	10.77	10.66

8		C	96–97	10	$C_{14}H_{22}N_2OS$	10.51	10.62
9		C	75–76	12	$C_{15}H_{23}N_3O$	16.09	15.95

[a] This yield is of slightly less pure material, m.p. 128–129.5°. The melting point reported above was obtained by recrystallization of this material once from a mixture of benzene and petroleum ether (b.p. 60–90°) and twice from methanol.

[b] R = $CH_2{=}CH(CH_2)_8CONH$—.


A
B
ArCOCl
H₂
Ni
H₂O
HCl
II
I

cylic acid (Table II, No. 3). The activity of the last compound was not surprising in view of the report by Hirt and Hurni (2) of the *in vitro* activity of several long chain amides of *p*-aminosalicylic acid. The activity must be due in part to the long chain fragment since *p*-acetaminosalicylic acid was reported essentially inactive *in vitro* by Doub and co-workers (3). None of the three compounds listed above was found effective when tested *in vivo* against experimental tuberculosis in mice and guinea pigs.

The remaining compounds showed no *in vitro* activity or were active at a concentration higher than 0.002 mg./10 ml.

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EXPERIMENTAL[4]

p-Nitro-10-hendecenamidobenzene. A mixture of 9.0 g. (0.065 mole) of *p*-nitroaniline and 10-hendecenoyl chloride (4) (prepared from 5.5 g. (0.03 mole) of 10-hendecenoic acid) in 15 ml. of benzene was heated under reflux for 12 hours. Benzene (100 ml.) was added and the resulting mixture filtered. The benzene was evaporated from the filtrate and the solid residue washed with dilute hydrochloric acid. The product was recrystallized from a mixture of water and acetone to give 7.5 g. (82%) melting at 67–68°. One recrystallization from petroleum ether (b.p. 60–90°) gave white needles melting at 71–71.5°.

Anal. Calc'd for $C_{17}H_{24}N_2O_3$: N, 9.21. Found: N, 9.27.

p-Aminohendecanamidobenzene. The above nitro compound (3 g., 0.01 mole) was dissolved in 50 ml. of 95% ethanol and treated with hydrogen over Raney nickel catalyst at 45 lbs. pressure for two hours. After removal of the catalyst, the filtrate was concentrated and cooled to give 2.5 g. (91%) of amine, m.p. 105–106°. Two recrystallizations from methanol gave a product melting at 107–107.5°.

Anal. Calc'd for $C_{17}H_{28}N_2O$: N, 10.16. Found: N, 10.40.

4-(p-Nitrobenzenesulfonamido)-1-(hendecanamido)benzene. Procedure A. A solution of 1.0 g. (0.0036 mole) of *p*-aminohendecanamidobenzene and 1.2 g. (0.0054 mole) of *p*-nitrobenzenesulfonyl chloride in 10 ml. of anhydrous pyridine was heated for four hours on a steam-bath. The resulting solution was poured into excess water and the precipitated solid (1.7 g.) removed by filtration. The product was recrystallized three times from 95% ethanol and once from acetone to give 1.6 g. (97%) of amide melting at 185–186°.

Anal. Calc'd for $C_{23}H_{31}N_3O_5S$: N, 9.11. Found: N, 9.02.

Procedure B. A solution of 3.5 g. (0.012 mole) of 4-(*p*-nitrobenzenesulfonamido)aniline (5) and 2.4 g. (0.012 mole) of hendecanoyl chloride in 15 ml. of pyridine was allowed to stand for two hours. After pouring into excess water, the precipitated solid was recrystallized once from petroleum ether (b.p. 60–90°) and twice from 95% ethanol to give 4.0 g. (73%) of product melting at 185–186°. A mixture m.p. with the amide prepared by the other route showed no depression.

Compounds 1–11 in Table I were prepared from 4-(*p*-nitrobenzenesulfonamido)aniline and the corresponding acid chloride in general accordance with Procedure B above. Compounds 12 and 13 were prepared from *p*-nitrobenzenesulfonyl chloride and the corresponding amine in general accordance with Procedure A above.

n-Octadecyl p-nitrobenzenesulfonate. The reaction of 40.5 g. (0.15 mole) of *n*-octadecanol and 49.5 g. (0.22 mole) of *p*-nitrobenzenesulfonyl chloride in 200 ml. of pyridine was carried out as described previously (6) for the preparation of *n*-octadecyl *p*-toluenesulfonate. This ester was obtained in 69% yield (47.0 g.) after recrystallization once from ethanol and twice from petroleum ether (b.p. 60–90°). The product melted at 96–97°.

Anal. Calc'd for $C_{24}H_{41}NO_5S$: S, 7.04. Found: S, 7.00.

[4] All melting points were taken on a Fisher melting point block and are uncorrected.

n-Octadecyl p-aminobenzenesulfonate. The nitro compound (10.0 g., 0.022 mole) in alcoholic solution was reduced at 45 lbs. hydrogen pressure over Raney nickel. The product was recrystallized once from ethanol, twice from petroleum ether, and twice more from ethanol to give 1.2 g. (28%) of the amide, m.p. 133–134°.

Anal. Calc'd for $C_{24}H_{43}NO_3S$: S, 7.53. Found: S, 7.66.

n-Octadecyl 4-(p-nitrobenzenesulfonamido)benzenesulfonate. The above amine (3 g., 0.0070 mole) and 1.8 g. (0.0081 mole) of *p*-nitrobenzenesulfonyl chloride were allowed to react by Procedure A. The product was recrystallized once from ethanol, twice from petroleum ether, and twice more from ethanol to give 1.2 g. (28%) of the amide, m.p. 133–134°.

Anal. Calc'd for $C_{30}H_{46}N_2O_7S_2$: S, 10.50. Found: S, 10.58.

p,p'-Di-10-hendecenamidobiphenyl. Procedure C. A mixture of 15 g. (0.058 mole) of benzidine dihydrochloride, 100 ml. of ether, and 14 g. of sodium carbonate was stirred while 67 g. (0.33 mole) of 10-hendecenoyl chloride was added slowly. The mixture was then stirred and heated under reflux (50°) for six hours. The mixture was cooled, poured into excess water, and acidified with 5% hydrochloric acid. The precipitated solid was removed and washed with dilute hydrochloric acid and water. It was recrystallized four times from glacial acetic acid with charcoal treatment to give 5.2 g. (17%) of white plates, m.p. 248–250°.

Anal. Calc'd for $C_{34}H_{48}N_2O_2$: N, 5.42. Found: N, 5.39.

Compounds in Table II marked "Procedure C" were made in general accordance with he above procedure.

SUMMARY

A series of twenty-seven amides of *p*-nitrobenzenesulfonic acid and 10-hendecenoic acid have been prepared and evaluated for antitubercular chemotherapeutic activity against the H37Rv strain of *M. tuberculosis*.

The following compounds were active *in vitro* at a concentration of 0.002 mg./10 cc. of test medium or lower: (a) 1-(*p*-nitrobenzenesulfonamido)-4-(3′,5′-dinitrobenzamido)benzene; (b) *p,p'*-bis(10-hendecenamido)diphenyl sulfone; and (c) *p*-(10-hendecenamido)salicylic acid.

Of the three compounds listed above, none was active *in vivo* in mice and guinea pigs.

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(2) HIRT AND HURNI, *Helv. Chim. Acta*, **32**, 378 (1949).
(3) DOUB, SCHAEFER, BAMBAS, AND WALKER, *J. Am. Chem. Soc.*, **73**, 903 (1951).
(4) ENGLISH AND VELICK, *J. Am. Chem. Soc.*, **67**, 1413 (1945).
(5) SHIRLEY AND SCHMIDT, *J. Am. Chem. Soc.*, **73**, 867 (1951).
(6) SHIRLEY AND REEDY, *J. Am. Chem. Soc.*, **73**, 458 (1951).