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SYNTHESIS AND BIOLOGICAL ACTIVITIES OF *TRANS*-Δ^9-HEXADECENYL UREA AND *TRANS*-Δ^2-UNDECENYL UREA

R. N. MAJEE, S. C. AGARWAL, S. N. MUKHERJEE* and J. N. CHATTERJEA**

Chemistry Division, Indian Lac Research Institute, Ranchi 834 010, India.

**Department of Chemistry, St. Xavier's College, Ranchi 834 001, India.*

***Visiting Professor, Magadh University, Bodh Gaya 824 231, India.*

ABSTRACT

Syntheses of *trans*-Δ^9-hexadecenyl urea (VI) and *trans*-Δ^2-undecenyl urea (X) have been achieved from *threo*-aleuritic acid (I), the major constituent (~ 30 %) of shellac. These compounds showed interesting biological activity.

INTRODUCTION

BARBITURATES are well-known for their wide range of biological activities[1] along with their therapeutic values. But these are five-membered ring compounds. Literature survey reveals that biological activities of such ureides having macrocyclic ring have not been studied so far. We have, therefore, attempted to synthesise the title compounds. The preliminary screening of their biological activities showed some interesting results and suggests further investigation including structural relationship which is in progress.

As the two ureides have been synthesised using two long chain unsaturated dioic acids, conveniently prepared from easily available natural product, *threo*-aleuritic acid[2], we attach much importance to their syntheses in case the biological activities show their therapeutic utility.

threo-9, 10-Dihydroxyhexadecane-1, 16-dioic acid (III) was prepared from *threo*-aleuritic acid (I) by oxidation of the isopropylidene derivative (II) of I with $KMnO_4$ followed by removal of isopropylidene group by acid treatment. III on treatment with ethyl orthoformate/benzoic acid at 170°C for 4 hr followed by alkaline hydrolysis (alcoholic) of the resultant product yielded hexadec-*trans*-9-ene dioic acid (IV). The acid chloride (V) was refluxed with urea in dry benzene for 4 hr to give (VI). Azelaic acid aldehyde (VII), one of the periodate oxidation products of I, on condensation with malonic acid in the presence of pyridine gave undec-*trans*-2-enedioic acid (VIII). The acid chloride (IX) was refluxed with urea in dry benzene to result (X). The courses of reactions involved in the above two syntheses are schematically shown below:

$HOH_2C.(CH_2)_5.CH(OH).CH(OH).(CH_2)_7.CO_2H \rightarrow$

I

$HOH_2C.(CH_2)_5.CH{-}CH.(CH_2)_7.CO_2H \rightarrow$ (the two CH groups joined through O–C(CH₃)₂–O, i.e. isopropylidene: O, O, C, H_3C, CH_3)

II

$HO_2C.(CH_2)_5.CH(OH).CH(OH).(CH_2)_7.CO_2H \rightarrow$

III

$HO_2C.(CH_2)_5.CH{=}CH.(CH_2)_7.CO_2H \rightarrow$

IV

$ClOC.(CH_2)_5.CH{=}CH.(CH_2)_7.COCl \rightarrow$

V

$OC.(CH_2)_5.CH{=}CH.(CH_2)_7.CO$ (both CO groups joined by NH–CO–NH)

VI

$OHC.(CH_2)_7.CO_2H \rightarrow$

VII

$HO_2C.HC{=}CH.(CH_2)_7.CO_2H \rightarrow$

VIII

$ClOC.HC{=}CH.(CH_2)_7.COCl \rightarrow$

IX

$OC.HC{=}CH.(CH_2)_7.CO$ (both CO groups joined by NH–CO–NH)

X

EXPERIMENTAL

threo-9-10-*Dihydroxyhexadecane*-1,16-*dioic acid (III)* —The title acid was obtained as a solid from *threo*-

aleuritic acid (m.p. 100–101°C; 5 g) following the procedure reported in literature[3], yield (3.5 g), m.p. 122–24°C. IR (KBr): 3250 (OH) 1700 (COOH) cm^{-1} (Found: C, 60.32; H, 9.41. Calcd. for $C_{16}H_{30}O_5$: C, 60.37; H, 9.43 %).

Hexadec-trans 9-ene dioic acid (IV)—*threo*-9,10-Dihydroxydecane-1,16-dioic acid (2.5 g), ethylorthoformate (5 ml) and benzoic acid (0.1 g) were mixed and arranged for distillation. The internal temperature of the reaction mixture was maintained at 70–80°C till no more ethanol (formed during the reaction) distilled. The temperature was then slowly raised to 170°C and maintained for 4 hr. After removing excess of ethylorthoformate under reduced pressure, the residue was refluxed with alcoholic KOH (25 ml; 10 %). The excess of alcohol was then removed *in vacuo* and acidified to yield a solid, which was filtered, washed with water and dried. On crystallisation from ethyl acetate, white needles of the desired enoic acid was obtained, yield (2.1 g), m.p. 101–3°C (lit.[4] m.p. 102–3°C); IR (KBr): No-OH absorption, 1700 (COOH), 970 (*trans* HC=CH) cm^{-1} (Found: C, 67.52; H, 9.82. Calcd. for $C_{16}H_{28}O_4$: C, 67.60; H, 9.85 %).

Acidchloride (V)—The foregoing unsaturated dioic acid (IV; 2 g) in dry benzene (10 ml) was refluxed with $SOCl_2$ (5 ml) for 4 hr. Removal of excess of solvent and $SOCl_2$ *in vacuo* yielded acid chloride as a liquid (2.1 g), which was purified over a column of silica gel using benzene as eluent. Purity of the compound was checked by TLC. IR (neat): 1800 (COCl), 970 (*trans* HC =CH) cm^{-1} (Found: Cl, 22.00, $C_{16}H_{26}O_2Cl_2$ requires Cl, 22.11.

trans-Δ^9-Hexadecenylurea (VI)—A solution of the above acidchloride (V; 2 g) in dry benzene (5 ml) was added to a well stirred boiling mixture of dry benzene (10 ml) and urea (2 g) and heated under reflux for 4 hr. Removal of benzene under diminished pressure gave a solid, which was washed sequentially with aq. sodium bicarbonate solution (25 ml; 5 %), water and dried. On crystallisation from methanol, needles of the title compound were obtained (1.6 g), m.p. 220°C (decomp.). IR (KBr): 3320 (–NH), 1700 (–CONH), 970 (*trans* HC=CH) cm^{-1} (Found: N, 9.00. $C_{17}H_{28}N_2O_3$ requires N, 9.10 %).

Azelaic acid aldehyde (VII)—*threo*-Aleuritic acid (8 g) was dissolved in methanol-water (400 ml; 1 : 1, v/v) by warming and a solution of sodium periodate (6 g) in 1(N) H_2SO_4 (300 ml) was added to it with vigorous stirring. After 10 min the reaction mixture was cooled to room temperature and extracted with ether. Ether extract was washed with aq. sodium bicarbonate solution (200 ml; 5 %). Acidification of the sodium extract yielded a liquid which was again taken up in ether. Ethereal layer was washed with brine solution and dried (Na_2SO_4). Removal of the solvent afforded azelaic acid aldehyde as a thick liquid (3.6 g), which was purified over a column of neutral alumina with ether as eluent. IR (neat): 1720 (CHO), 1700 (COOH) cm^{-1} (Found: C, 62.73; H, 9.24. Calcd. for $C_9H_{16}O_3$: C, 62.79; H, 9.30 %).

Undec-trans-2-enedioic acid (VIII)—The above acid aldehyde (VII; 3.5 g) was heated on a steam-bath with malonic acid (3.5 g) in the presence of dry pyridine (10 ml) till CO_2 evolution ceased. On usual work-up with ether, a solid was obtained, which on crystallisation from ethyl acetate gave white needles of the title acid, yield (2.7 g), m.p 95–97°C. IR (KBr): 1700 (COOH), 970 (*trans* HC=CH) cm^{-1} (Found: C, 61.62; H, 8.40. $C_{11}H_{18}O_4$ requires C, 61.67; H, 8.41 %).

Acid chloride (IX)—Treatment of the foregoing acid (VIII; 3 g) in dry benzene (10 ml) with $SOCl_2$ and following the procedure described earlier, the acid chloride was obtained as a liquid (2.8 g). IR (neat): 1800 (COCl), 970 (*trans* HC =CH) cm^{-1} (Found: Cl, 28.24. $C_{11}H_{16}O_2Cl_2$ requires Cl, 28.28 %).

trans-Δ^2-Undecenyl urea (X)—The above acid chloride (2 g) was heated under reflux with urea (2 g) in dry benzene (5 ml) for 4 hr and worked up as before to yield the desired cyclic ureide, which crystallised from methanol, yield (1.6 g), m.p. 222–24°C. IR (KBr): 3325 (–NH), 1700 (–CONH), 970 (*trans* HC=CH) (Found: N, 11.74. $C_{12}H_{18}N_2O_3$ requires N, 11.76 %).

Bio-Assay

Preliminary screening of *trans*-Δ^9-hexadecenyl urea (VI) and *trans*-Δ^2-undecenyl urea (X) showed no gross behavioural effects upto dose levels of 500 mg/kg body weight when administered intraperitoneally (i.p.) to

Table 1 *Biological activities of trans-Δ^9-hexadecenyl urea and trans-Δ^2-undecenyl urea*

Compound	Observations
trans-Δ^9-hexa-decenyl urea	(i) Q Wave absent (ii) S. T. Segment depressed (iii) T. Wave irregular
trans-Δ^2-undecenyl urea	(i) T. P. interval less than control (ii) S. T. Segment depressed (iii) QRS complex irregular

mice. However, these compounds at the same dose level of 500 mg/kg body weight when administered intraperitoneally (i.p.) elicited electrocardiographic changes in mice and the observations are given in table 1.

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