whereas with the other two aldehydes no definite product could be isolated. The infrared absorption spectrum of (VI) showed bands at 2.97 μ (—OH groups); 3 to 4.5 μ (broad absorption of NH group); 6.23 μ (COOH); 5.53 μ (aromatic ring); 8.23 μ (strong band from phenolic OH).

EXPERIMENTAL

General method of condensation of α-keto acids with 2,3- and 3,4-dihydroxy-β-phenethylamines. To a solution of 1 mmole of the amine hydrobromide in a minimum quantity of water, 1.2 mmoles of the α-keto acid dissolved in 3–4 ml. of dioxane or water was added. The *p*H of the solution was then adjusted from 4 to 6 as required by the addition of dilute ammonia. Crystalline solids usually separated in 48–96 hr., sometimes less. Where no solid separated, concentration of the solution under reduced pressure at room temperature gave the desired isoquinolines. The latter could be crystallized with difficulty from dilute acetic acid.

1-Hydroxymethyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline and its dimethylether, dl-Calcotomine. A solution of 168 mg. of homoisovanillylamine and 132 mg. of glycollic aldehyde in 5 ml. water was adjusted to *p*H 5 and kept at 30° for 70 hr. The mixture was made alkaline by addition of bicarbonate and repeatedly extracted with chloroform. Removal of the solvent yielded a brownish solid which after several crystallizations from chloroform gave 30 mg. of colorless needles, m.p. 200–201°.

Anal. Calcd. for $C_{11}H_{15}O_3N$: C, 63.2; H, 7.1; N, 6.7. Found: C, 62.9; H, 6.8; N, 6.5.

Methylation of the above with diazomethane yielded a solid which on crystallization from ethylacetate gave m.p. 133°.

Anal. Calcd. for $C_{12}H_{17}O_3N$: C, 64.5; H, 7.6; N, 6.2. Found: C, 64.6; H, 7.2; N, 6.3.

The hydrochloride from the above had m.p. 194°.

Anal. Calcd. for $C_{12}H_{18}ClO_3N$: Cl, 13.7. Found: Cl, 13.4.

3-Carboxy-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline. A solution of 197 mg. of DOPA in 10 cc. of water was added to 0.17 cc. of 35% formaldehyde solution. The *p*H of the mixture was found to be 6. It was kept at 30° for 72 hr. The brownish solid which separated was filtered and crystallized from water in colorless needles, m.p. 277°. Yield, 115 mg.

Anal. Calcd. for $C_{10}H_{11}O_4N$: C, 57.4; H, 5.3; N, 6.6. Found: C, 57.2; H, 5.6; N, 6.7.

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The Synthesis of Pyrimidine Analogs of Xylocaine

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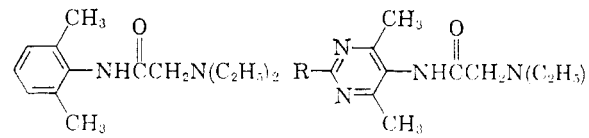
α - Diethylamino - 2,6 - dimethylacetanilide[1] (Xylocaine) (I) and similar compounds were found to be highly effective local anesthetics. In this work, several compounds (II, III), closely related in structure to I, were prepared in which the benzene ring was replaced by a pyrimidine ring. Compounds II and III showed little activity when tested as local anesthetics; they were also inactive as antispasmodics when tested on isolated guinea pig ileum and produced no hypnosis in rats.



I

II. R = CH_3
III. R = NH_2

The condensation of acetamidine or guanidine with benzeneazoacetylacetone gave the corresponding 5-benzeneazopyrimidines (IV, V) which were then catalytically reduced to give 2,4,6-trimethyl-5-aminopyrimidine (VI) and 2,5-diamino-4,6-dimethylpyrimidine (VII).[2] Acylation of VI and VII with one equivalent of chloroacetyl chloride and subsequent reaction with diethylamine resulted in 2,4,6-trimethyl-5-α-diethylaminoacetamidopyrimidine (II) and 2-amino-4,6-dimethyl-5-α-diethylaminoacetamidopyrimidine (III).

EXPERIMENTAL[3]

2,4,6-Trimethyl-5-benzeneazopyrimidine (IV). A solution of 8.5 g. sodium in 160 ml. of ethanol was added to a solution of 50 g. of benzeneazoacetylacetone and 35 g. of acetamidine hydrochloride in 900 ml. of ethanol. The solution was filtered from the sodium chloride and allowed to stand for 2 weeks. Evaporation of the alcohol and then addition of a dilute sodium hydroxide solution gave a sticky solid. Recrystallization from alcohol-water and then petroleum ether (b.p. 60–90°) gave 8 g. of orange plates, m.p. 125–126°.

Anal. Calcd. for $C_{13}H_{14}N_4$: C, 69.00; H, 6.24. Found: C, 69.04; H, 6.12.

2,4,6-Trimethyl-5-aminopyrimidine (VI). A suspension of 3.0 g. of 10% palladium on charcoal in a solution of 4.5 g. of 2,4,6-trimethyl-5-benzeneazopyrimidine (V) in 60 ml. of ethanol was hydrogenated at 100° under a pressure of 1000 p.s.i. The reaction mixture was filtered from the catalyst, the solvent evaporated *in vacuo*, and the product recrystallized from benzene giving 2.3 g. of pale yellow crystals, m.p. 174–175°.

Anal. Calcd. for $C_7H_{11}N_3$: C, 61.28; H, 8.08; N, 30.62. Found: C, 62.01; H, 8.28; N, 30.36.

2,4,6-Trimethyl-5-α-chloroacetamidopyrimidine (VIII).[4] To a cold mixture of 1.1 g. of 2,4,6-trimethyl-5-aminopyrimidine (VI) in glacial acetic acid was added 1.1 ml. of chloroacetyl chloride. After several minutes, the solution was diluted with benzene and the acid neutralized by the addition of solid sodium carbonate. The benzene solution was filtered from the solid and the solvent removed *in vacuo*. Recrystallization

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(2) R. Hull, B. Lowell, H. Openshaw, and A. Todd, *J. Chem. Soc.*, 41 (1947).

(3) All melting points were uncorrected.

(4) This compound has been reported, but no data as to its preparation or properties were given: R. Thomson, M. Wilkens, G. Hitchings, and P. Russell, *Proc. Soc. Expt. Biol. Med.*, **72**, 169 (1949).

of the residue from petroleum ether–benzene gave 1.4 g. of long white needles, m.p. 155–156°.

Anal. Calcd. for $C_9H_{12}ClN_3O$: N, 19.66. Found: N, 20.07.

2-Amino-4,6-dimethyl-5-α-chloroacetamidopyrimidine (IX) was prepared from 1.0 g. of 2,5-diamino-4,6-dimethylpyrimidine[2] (VII) and 0.82 g. of chloroacetyl chloride in 6 ml. of acetic acid and the product precipitated by the addition of a sodium acetate solution.

Recrystallization from water gave 1.4 g. of long white needles, m.p. 226–227°.

Anal. Calcd. for $C_8H_{11}ClN_4O$: C, 44.76; H, 5.17. Found: C, 44.88; H, 5.30.

2,4,6-Trimethyl-5-α-diethylaminoacetamidopyrimidine (II). A solution of 1.0 g. of 2,4,6-trimethyl-5-α-chloroacetamidopyrimidine (VIII) and 2 ml. of diethylamine in ethanol was refluxed for 5 hr. and then the solvent removed *in vacuo*. The product was extracted with benzene and precipitated by the addition of petroleum ether. Recrystallization from petroleum ether gave 0.9 g. of white crystals, m.p. 156–157°.

Anal. Calcd. for $C_{13}H_{22}N_4O$: N, 22.38. Found: N, 22.39.

2-Amino-4,6-dimethyl-5-α-diethylaminoacetamidopyrimidine (III). A solution of 1.0 g. of 2-amino-4,6-dimethyl-5-α-chloroacetamidopyrimidine (IX) and 1.2 g. of diethylamine in 40 ml. of ethanol was refluxed for 5 hr. after which the solvent was evaporated and the product precipitated by the addition of dilute alkali. Recrystallization from water gave white prisms (80% yield), m.p. 209–210°.

Anal. Calcd. for $C_{12}H_{21}N_5O$: C, 57.34; H, 8.42. Found: C, 57.53; H, 8.56.

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Synthesis of Vitamin A *p*-Phenylsulfonylbenzoate[1]

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Although numerous vitamin A derivatives have been reported in the literature[3,4,5] only a small number of these have been successfully used in the isolation and purification of small quantities of vitamin A from biological materials. For our degradation studies with biologically synthesized labeled vitamin A it is desirable to have a crystalline derivative of vitamin A which can be purified by crystallization and which contains the vitamin A molecule essentially intact. It is also necessary to have a derivative which will yield upon oxidation and steam distillation only the desired acidic degradation of products of vitamin A (*e.g.*, acetic acid and carbon dioxide). Examination of various vitamin A derivatives indicated that the ester form would satisfy the first requirement. However, none of the known ester derivatives appeared entirely suitable.

As most organic sulfones are crystalline solids and are easily crystallized, *p*-phenylsulfonylbenzoic acid was selected for investigation. The acid chloride of the above acid reacted with vitamin A to yield a white, crystalline solid. The ultraviolet spectrum of this compound exhibited the characteristic peak for vitamin A at 325 mμ and a second peak at 246 mμ indicating the presence of a sulfone group. The infrared spectra showed a strong absorption peak at 5.81 μ, which is characteristic of the ester linkage. Determination of the vitamin A component of the ester by the Carr-Price reaction[6] indicated that 51% (theoretical 51.5%) of the molecule was vitamin A. Furthermore, the experimental molecular weight of the ester was in agreement with the calculated molecular weight. Using this derivative it has been possible to isolate successfully and purify vitamin A from a 1:1 mixture of cholesterol and vitamin A.

EXPERIMENTAL

Melting points are uncorrected. *p*-Tolyl phenyl sulfone, *p*-phenylsulfonylbenzoic acid and *p*-phenylsulfonylbenzoyl chloride were prepared according to the procedure of Newell.[7]

Vitamin A p-phenylsulfonylbenzoate. *p*-Phenylsulfonylbenzoyl chloride (500 mg., 1.78 mmoles) was added to 30 ml. of dichloromethane in a two-necked flask equipped with reflux condenser and inlet tube for nitrogen. Dry pyridine (0.5 ml.) was added to the solution followed by 100 mg. (0.35 mmole) of vitamin A. The solution was mixed and heated at 52° for 5 hr. under nitrogen. The solution was evaporated to dryness under nitrogen and extracted three times with a mixture of petroleum ether (b.p. 37°) and dichloromethane (10/3, v./v.). The combined extracts were washed with 50 ml. of 1% sodium bicarbonate solution, 100 ml. of water, and dried over anhydrous sodium sulfate. The solution was taken to dryness under nitrogen and the solid extracted four times with 60 ml. of boiling petroleum ether (b.p. 37°). The extracts were combined in an Erlenmeyer flask, flushed with nitrogen, stoppered, and cooled to 0° for 16 hr. The resulting white crystals of vitamin A *p*-phenylsulfonylbenzoate (80% yield) after one recrystallization from petroleum ether (b.p. 37°) melted at 80–82°.

Anal. Calcd. for $C_{33}H_{38}SO_4$; C, 74.7; H, 7.2; mol. wt., 530. Found: C, 74.3; H, 6.9; mol. wt., 535; $E^{1\%}_{1\,cm}$ = 985 (325 mμ. petroleum ether).

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(2) From the Master's thesis of C. K. Payne, West Virginia University Medical Center, Morgantown, W. Va.

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