was then bubbled into this mixture and the amount added was controlled by weighing the total assembly. After hydrogen bromide addition, the solution was visibly homogeneous. This mixture was then brought to reaction temperature, and the contents sampled as a function of time, by means of a hypodermic syringe inserted through the neoprene diaphragm. The sample was injected into ice water, worked up, and analyzed by a combination of infrared, mass spectrometric, and gas liquid partition chromatographic techniques. The analytical technique was estimated to be accurate to within ±5% at C_{10} aromatic values below about 15%. Above 15%, higher molecular weight materials were formed and these are included in the C_{10} aromatic values.

The outlet of the reflux condenser was connected to a gas collecting device. Only traces of gas were evolved during the experiments reported in this paper.

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Heterocyclic Compounds. I. Synthesis of Some Isoquinoline Derivatives

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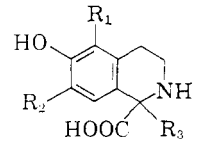
In connection with the synthesis of isoquinoline derivatives, we investigated the conditions of the Pictet-Spengler reaction[1] involving the condensation of β-phenethylamine derivatives with different α-keto acids and aldehydes.

The condensation of 2,3-dihydroxy-β-phenethylamine (B) with phenylpyruvic acid, α-keto-*n*-valeric acid and 3,4-dimethoxyphenylpyruvic acid in dioxane medium afforded the corresponding isoquinoline derivatives. With pyruvic acid or α-ketoglutaric acid, B failed to give any definite products.



I. R_1 = H; R_2 = OH; R_3 = C_3H_7
II. R_1 = H; R_2 = OH; R_3 = 3,4-$(OCH_3)_2CH_2C_6H_5$
III. R_1 = OH; R_2 = H; R_3 = $CH_2C_6H_5$
IV. R_1 = OH; R_2 = H; R_3 = C_3H_7
V. R_1 = OH; R_2 = H; R_3 = 3,4-$(OCH_3)_2CH_2C_6H_5$

The condensation of 3,4-dihydroxyphenylalanine (DOPA) with pyruvic, phenylpyruvic, or α-keto-*n*-valeric acid did not seem to occur.

With a view to synthesize the alkaloid calycotomine, isolated from the Australian plant Calycotome Spinosa Link (Leguminosae) by E. P. White,[2] the condensation of A with glycollic aldehyde was attempted under different conditions of *p*H and time. However, no pure product could be isolated in any case.

When the reaction of 3-hydroxy-4-methoxy-β-phenethylamine[3] with glycolic aldehyde was carried out in aqueous medium at *p*H 5 for seventy hours 1-hydroxymethyl-6-hydroxy-7-methoxy-1,2,-3,4-tetrahydroisoquinoline was obtained in poor yield. The latter on methylation with diazomethane afforded the dimethyl ether, *dl*-Calycotomine.

The latter has been synthesized also by A. Chatterjee[4] and by Battersby and co-workers.[5]

With DOPA the condensation of glycolic aldehyde was unsuccessful. It was, therefore, thought of interest to investigate the reaction of formaldehyde, acetaldehyde, and anisaldehyde with DOPA under different conditions. Only with formaldehyde, the desired 3 - carboxy - 6,7 - dihydroxy - 1,2,3,4 - tetrahydroisoquinoline (VI) was obtained

Isoquinoline	*p*H	Time in Hours	M.P.	Yield, %	Formula	Found C, %	Found H, %	Found N, %	Calcd. C, %	Calcd. H, %	Calcd. N, %
I	6	96	226	55	$C_{13}H_{17}O_4N$	61.9	6.5	5.9	62.14	6.82	5.6
II	6	96	229–230	70	$C_{19}H_{21}O_6N$	63.2	5.8	4.3	63.5	5.9	4.0
III	6	72	244–245	60	$C_{17}H_{17}O_4N$	67.9	5.6	4.5	68.21	5.73	4.7
IV	4	50	242	60	$C_{13}H_{17}O_4N$	62.3	6.9	5.8	62.14	6.82	5.6
V	4	100	234–236	65	$C_{19}H_{21}O_6N$	63.2	5.6	4.0	63.5	5.9	4.0

The condensation of 3,4-dihydroxy-β-phenethylamine (A) with α-keto-*n*-valeric acid in aqueous solution at *p*H 5-6 afforded 1-carboxy-6,7-dihydroxy-1-propyl-1,2,3,4-tetrahydroisoquinoline (I). Because of the lower solubility of 3,4-dimethoxyphenylpyruvic acid in water, the reaction with A was carried out in dioxane medium when the isoquinoline (II) was formed. In general, when the condensations were run in a dioxane medium, the isoquinoline derivatives separated from solution more rapidly and in purer form. Attempts to condense A with dimethylpyruvic acid, oxalacetic acid, and the sodium salt of oxalacetic ester under different conditions proved unsuccessful.

(1) W. M. Whaley and T. R. Govindachari, *Org. Reactions*, **VI**, p. 151 (1951).
(2) E. P. White, *New Zealand J. Sci. Tech.*, **25B**, 152 (1954); **33B**, 38 (1951).
(3) K. E. Hamlin and F. E. Fischer, *J. Am. Chem. Soc.*, **75**, 5119 (1953).
(4) A. Chatterjee and N. A. Chaudhury, *Sci. and Culture*, **25**, 389 (1959).
(5) A. R. Battersby and T. P. Edwards, *J. Chem. Soc.*, 1909 (1959).

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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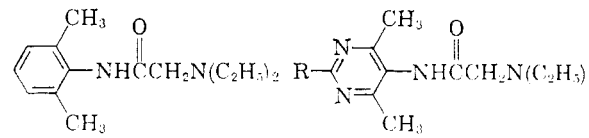
α - Diethylamino - 2,6 - dimethylacetanilide[1] (Xylocaine) (I) and similar compounds were found to be highly effective local anesthetics. In this work, several compounds (II, III), closely related in structure to I, were prepared in which the benzene ring was replaced by a pyrimidine ring. Compounds 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

(1) N. Lofgren, *Arkiv. Kemi, Mineral. Geol.*, **A22**, No. 18 (1946); *Chem. Abstr.*, **43**, 1021 (1949).

(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).