Chem. Abs. 47, 3299-3300 (1953)

Utilization of safrole as a medical raw material. V. Syntheses of imidazole and thiazole compounds. Masao Ohara (Inst. Pharmaceutical Resources, Koganei, Tokyo). *J. Pharm. Soc. Japan* **72**, 936–8(1952); cf. *C.A.* **46**, 11206*h*. —3,4-$CH_2O_2C_6H_3CH(OMe)CH(NH_2)Me$ (I) (1 g.), 1.3 g. $PhCH_2C(OEt):NH.HCl$, and 0.5 g. Na_2CO_3 in 10 ml. Et_2O mixed well, allowed to stand overnight, water and Et_2O added, the Et_2O layer distd., the sirupy residue dissolved with alc. HCl, filtered, and the filtrate cooled give 1.1 g. 3,4-$CH_2O_2C_6H_3CH(OMe)CHMeNHC(:NH)CH_2Ph$ (II), white plates, decomp. 250–1° (from dil. alc.). 3,4-$CH_2O_2C_6H_3COCHBrMe$ (III) (2 g.), 1 g. $MeC(:NH)NH_2.HCl$, and 3 g. Na_2CO_3 fused 2 hrs. at 160°, cooled, heated with dil. HCl, filtered, the filtrate made alk. with NH_4OH, the oily layer extd. with AcOEt, the AcOEt removed, and the residue treated with MeOH-HCl give 2,5-dimethyl-4-(3,4-methylenedioxyphenyl)imidazole (IV); IV.HCl, decomp. 227–9°. III (3 g.), 3 g. $PhCH_2C(:NH)NH_2.HCl$, and 4 g. AcONa heated 4 hrs. at 150–60°, cooled, dil. HCl added, the mixt. filtered, the filtrate made alk. with NH_4OH, the oily layer extd. with C_6H_6, the C_6H_6 removed, and the residue treated with MeOH-HCl give 4-(3,4-methylenedioxyphenyl)-5-methylimidazole (V); V.HCl.0.5H_2O, white needles, decomp. 227–30°. III (10 g.) and 3 g. $(NH_2)_2CS$ in 100 ml. hot alc. allowed to stand overnight give 2-amino-4-(3,4-methylenedioxyphenyl)-5-methylthiazole as its HBr salt (VI), m. 207–10°, which, dissolved in a large amt. of water, made alk., and the ppt. filtered and recrystd. from alc. gives 7.6 g. of the free base (VII), plates, m. 185–6°; VII.HCl, needles, decomp. 224–5°. VII (3 g.) in 30 ml. C_5H_5N treated with 3 g. *p*-$AcNHC_6H_4SO_2Cl$ portionwise, boiled 10 hrs. on an oil bath, the solvent removed *in vacuo*, the residue treated with dil. NaOH in excess, the insol. portion filtered, acidified, and the ppt. filtered, washed with water, and recrystd. from C_5H_5N-EtOH gives 3 g. 2-(*p*-$AcNHC_6H_4SO_2NH$) analog (VIII) of VII, granules, m. 216–17°; 2 g. VIII in 40 ml. EtOH-H_2O (1:1) contg. 10% NaOH, boiled on a water bath 2 hrs., water added, the alc. removed, the residue filtered, the filtrate made to pH 5 with dil. AcOH, and the product filtered and recrystd. from alc. give 15 g. 2-(*p*-$H_2NC_6H_4SO_2NH$) analog (IX) of VIII, needles, m. 219–21°. VII (2 g.) in 20 ml. xylene heated 7 hrs. with 3 g. $Et_2NCH_2CH_2Cl$ on an oil bath, the xylene removed *in vacuo*, the residue treated with dil. AcOH, filtered, the filtrate made alk., the oily layer extd. with C_6H_6, and the C_6H_6 removed give a sirupy 2-$Et_2NCH_2CH_2NH$ analog (X) of VII (picrolonate, decomp. 156–7°; picrate, m. 94–7°; methiodide, gelatinous).

VI. Syntheses of isoquinoline compounds having a dialkylaminoethyl radical. Masao Ohara, Kozo Mochizuki, and Yoshio Deguchi. *Ibid.* 939–41.—*o*-$PhCH_2OC_6H_4COCl$ (XI) (prepd. from $SOCl_2$ and the acid) condensed with I to sirupy *o*-[3,4-$CH_2O_2C_6H_3CH(OMe)CHMeNHCO]C_6H_4OCH_2Ph$-*o* (XII); 5 g. XII in 30 ml. xylene boiled 1 hr. with 9 g. $POCl_3$, cooled, petr. ether added, the clear upper layer decanted, the residue dissolved in MeOH, filtered with C, and the filtrate made alk. with NH_4OH gives sirupy 1-(*o*-benzyloxyphenyl)-3-methyl-6,7-methylenedioxyisoquinoline (XIII); 1-(*m*-benzyloxyphenyl) isomer (XIV), m. 115–17°. XIII (2.5 g.) in 30 ml. 20% HCl with a small amt. of MeOH heated on a water bath 4 hrs., filtered with C, the filtrate treated with Na_2CO_3, the ppt. filtered, treated with dil. NaOH, the insol. portion filtered off, the filtrate treated with satd. NH_4Cl, and the ppt. filtered and recrystd. from alc. give 1 g. 1-(*o*-HOC_6H_4) analog (XV) of XIII, plates, m. 146°; 1-(*m*-HOC_6H_4) isomer, plates, m. 268°. XV (0.7 g.), 3.5 g. 2% EtONa, and $Et_2NCH_2CH_2Cl$ with a trace of NaI boiled on a water bath 4 hrs., cooled, the ppt. filtered off, the filtrate concd. *in vacuo*, the oily layer extd. with C_6H_6, the ext. treated with dil. HCl, the HCl layer made alk., the oily layer taken up with C_6H_6, and the C_6H_6 removed give 0.6 g. sirupy 1-(*o*-$Et_2NCH_2CH_2OC_6H_4$) analog (XVI) of XV; picrate, needles, m. 184–6°; methiodide, gelatinous. 1-(*m*-$Et_2NCH_2CH_2OC_6H_4$) analog (XVII), sirupy; XVII picrate, m. 161–2°; XVII.MeI, granules, m. 75°; XVII.MeBr, gelatinous. 1-(*p*-$Et_2NCH_2CH_2OC_6H_4$) analog (XVIII) of XV, sirupy; picrate, decomp. 238–9°; methiodide, needles, m. 120°. Similarly, 0.7 g. XV and 0.3 g. $Me_2NCH_2CH_2Cl$ give a sirupy 1-(*o*-$Me_2NCH_2CH_2OC_6H_4$) analog (XIX) of XV; picrate, needles, m. 158–61°; methiodide, gelatinous. 1-(*m*-$Me_2NCH_2CH_2OC_6H_4$) analog (XX) of XV, sirupy; picrate, m. 190–2°; methiodide, leaves, m. 140°. 1-(*p*-$Me_2NCH_2CH_2OC_6H_4$) analog (XXI) of XV, solid; picrate, m. 207–11°. Me 1-methyl-6,7-methylenedioxy-3-isoquinolinecarboxylate (XXII) (1 g.) and 1 g. $Et_2NCH_2CH_2OH$ heated on an oil bath 6 hrs. at 150°, the volatile substance removed *in vacuo*, the residue taken up in 3% AcOH, filtered, the filtrate made alk., and the free base filtered and recrystd. from Me_2CO give the $Et_2NCH_2CH_2$ ester of XXII, $C_{18}H_{22}O_5N_2.0.5H_2O$, white needles, m. 69–71°. K. Kitsuta