in the formation of *S*-(+)-3-phenylbutyric acid and, furthermore, when this reaction was catalyzed by catalytic amounts of cuprous or cupric chlorides, the reaction products had the *R*-(−)-configuration.

3-Phenylbutyric Acid

Run	Catalyst [a]	% Yield	$[\alpha]^{25}_{D}$ [b]	% Optical [c] yield
1	—	46.1	+3.1°	5.4
2	Cu_2Cl_2	63.5	−5.9	10.2
3	—	53.0	+3.7	6.9
4	Cu_2Cl_2	60.1	−3.4	6.0
5	—	57.9	+3.3	5.9
6	Cu_2Cl_2	62.6	−3.6	6.3
7	$CdCl_2$	50.2	+4.6	8.1
8	$HgCl_2$	44.7	+2.5	4.4
9	Hg_2Cl_2	38.3	+3.7	6.5
10	AgCl	31.5	+2.9	5.1
11	$PtCl_4$	40.8	+2.5	4.4
12	$PdCl_2$	42.6	+3.6	6.4
13	Cu_2Cl_2 [d]	7.7	+0.87	1.5
14	$CuCl_2$	44.5	−3.6	6.3

a) 3 mole % catalyst used.
b) Solvent: benzene.
c) Calculated on −57° of the optically pure enantiomer (H. Rupe, *Ann.*, **369**, 335 (1909)).
d) Inverse addition i.e. addition of phenylmagnesium bromide to (−)-menthyl crotonate solution containing cuprous chloride.

This shows that the steric course of the reaction was altered by the presence of copper chlorides. In contrast to copper chlorides, other double-bond complexing agents such as Hg, Ag, Pt, Pd and Cd chlorides did not alter the stereoselectivity of this reaction and, even with cuprous chloride, when this reaction was carried out in an inverse manner, no catalyst effect was observed, the *S*-(+)-acid being the product.

Syntheses of 1-Phenyl-2-thiobarbituric Acid Derivatives and their Analgesic Activity

Jutaro Okada, Hajime Fujimura and Yoshiko Ueda

Yakugaku Zasshi (*Journal of the Pharmaceutical Society of Japan*) **82**, 976 (1962)

5-Alkylamino-2-thiobarbituric acid derivatives containing a *p*-substituted phenyl group in the nitrogen were synthesized in order to examine the presence of analgesic action in a compound by the introduction of two kinds of two kinds

of atom group, one having a pyrolytic and other hypnotic activity, in one molecule. Attempt for further introdction of an alkyl group in the carbon atom at 5-position failed. Pharmacological test of 19 kinds of the barbituric acid derivatives synthesized showed that none of them had a strong analgesic action.

Syntheses of Analgesics. (XXVIII)

Syntheses and Pharmacological Action of Isoxazole Derivatives. (1)

Torizo TAKAHASHI, Hajime FUJIMURA, and Atsushi ASAI

Yakugaku Zasshi (*Journal of the Pharmaceutical Society of Japan*), 82, 474 (1962)

Reaction of 3,4-dimethyl-5-aminoisoxazole with 2-haloacyl halide afforded 3,4-dimethyl-5-(2-haloacylamido) isoxazole and its reaction with dimethylamine, diethylamine, piperidine, and morpholine gave the corresponding amine compounds. Reaction of 3,4-dimethyl-5-aminoisoxazole with *p*-nitrobenzoyl chloride 3,4-dimethyl-5-(4-nitrobenzamido) isoxazole, which was catalytically reduced at ordinary pressure to 3,4-dimethyl-5-(4-aminobenzamido) isoxazole, and its reaction with 2-haloacyl halide afforded haloacyl compounds. Condensation of these compounds with various amines gave the corresponding amine compounds. Toxicity and analgesic activity of these new compounds were examined.

Syntheses of Analgesics. (XXIX)

Syntheses and Pharmacological Action of Isoxazole Derivatives. (2)

Torizo TAKAHASHI, Hajime FUJIMURA, and Atsushi ASAI

Yakugaku Zasshi (*Journal of the Phamaceutical Society of Japan*) 82, 481 (1962)

Reaction of metallic sodium and 2-alkoxyethyl bromide on acetonitrile afforded 2-(2-alkoxyethyl)-3-iminobutyronitrile which was condensed with hydroxylamine hydrochloride to prepare 3-methyl-4-(2-alkoxyethyl)-5-aminoisoxazole. Its reaction with 2-haloacyl halide to form the haloacyl compound and condensation with dimethylamine, diethylamine, and morphine afforded the corresponding amino derivatives.

Application of *p*-nitrobenzoyl chloride to 3-methyl-4-(2-alkoxyethyl)-5-aminoisoxazole afforded 3-methyl-4-(2-alkoxyethyl)-5-(4-nitrobenzamido) isoxazole which was submitted to catalytic reduction at ordinary pressure to prepare 3-methyl-4-(2-alkoxyethyl)-5-(4-nitrobenzamido) isoxazole.

Toxicity and analgesic action of these new compounds were examined.
