of the acetonitrile by ethyl acetate; 1.22-g. yield (53.5%), m.p. 158.5–160.5°. The C^{14}-labeled protected tripeptide was prepared by the carbodiimide method also.[1a]

Glycyl-α-aminoisobutyryl-L-alanine.—Hydrogen was passed through a solution of 1.37 g. (0.03 mole) of the protected tripeptide in 50 ml. of absolute ethanol containing 2.0 ml. of glacial acetic acid for 4 hr. in the presence of 0.5 g. of fresh palladium black with agitation by means of a Vibro-Mixer.[9] The product was obtained as shiny plates and recrystallized from water–acetone; 0.66-g. yield (95%), m.p. 238.5–240° dec., $[\alpha]^{26}D$ −26.3° (*c* 0.457, 1 *N* HCl); R_f 0.34 in 2-butanol–formic acid–water (75:15:10) and 0.70 in phenol–water (80:20), descending 15 hr., Whatman No. 1 paper.

Anal. Calcd. for $C_7H_{17}N_3O_4$: C, 46.74; H, 7.41; N, 18.17. Found: C, 46.78; H, 7.56; N, 17.57.[10]

The C^{14}-labeled free tripeptide was prepared by a similar procedure; specific activity was 16.8 μc./mmole.[1a]

Carbobenzoxyglycyl-α-aminoisobutyryl-L-valine Benzyl Ester.—To a solution of 1.47 g. (0.005 mole) of carbobenzoxyglycyl-α-aminoisobutyric acid in 100 ml. of acetonitrile was added 1.03 g. (0.005 mole) of dicyclohexylcarbodiimide; the mixture was stirred at room temperature for 1 hr. A fresh filtered solution of L-valine benzyl ester in acetonitrile [from 1.83 g. (0.005 mole) of L-valine benzyl ester benzenesulfonate and 0.75 ml. (0.005 mole) of triethylamine] was added; stirring was continued for 20 hr. at room temperature. The acetonitrile was removed *in vacuo*, and the residue was taken up in ethyl acetate and worked up as usual. Recrystallization from hot absolute ethanol and ethanol–ether yielded 1.60 g. (66%) of protected tripeptide, m.p. 114–116.5°, $[\alpha]^{26}D$ −26.7° (*c* 0.457, ethanol). A portion was recrystallized from ethanol–ether for analysis, m.p. 115.5–118°.

Anal. Calcd. for $C_{26}H_{33}N_3O_6$: C, 64.58; H, 6.88; N, 8.69. Found: C, 64.66; H, 6.98; N, 8.59.

Glycyl-α-aminoisobutyryl-L-valine.—Catalytic hydrogenolysis was carried out as described above on 0.97 g. (0.002 mole) of the protected tripeptide. To remove any acetate associated with the free tripeptide obtained, the product was dissolved in 20 ml. of water containing a sixfold molar excess of ammonia, lyophilized, redissolved in water, and lyophilized three more times. Recrystallization from water–alcohol–acetone yielded 0.50 g. (96%) of shiny plates, m.p. 240.5–241.5°, $[\alpha]^{26}D$ −11.0° (*c* 1.486, 1 *N* HCl); R_f 0.49 in 2-butanol–formic acid–water (75:15:10) and 0.86 in phenol–water (80:20), descending 15 hr.

Anal. Calcd. for $C_{11}H_{21}N_3O_{24}$: C, 50.95; H, 8.94; N, 16.21. Found: C, 50.99; H, 8.70; N, 16.02.

(9) The Vibro-Mixer was obtained from Fisher Scientific Co.

(10) A second portion of the carbobenzoxytripeptide benzyl ester was dissolved in methanol and subjected to hydrogenolysis as above, but in the absence of acetic acid. The melting point of the free tripeptide obtained was identical with that of the analytical sample and with that of an equal mixture of the two preparations.

3,6-Bis-*p*-dimethylaminobenzylidene-2,5-diketopiperazine[1]

CARL TABB BAHNER AND WILLIAM LONGMIRE

Carson-Newman College, Jefferson City, Tennessee

Received August 19, 1964

In preparing compounds containing systems of conjugated double bonds by reaction of dialkylaminobenzaldehyde with suitable ring compounds,[2] we attempted unsuccessfully to condense *p*-dimethylaminobenzaldehyde with 2,5-diketopiperazine. The desired compound was obtained, however, by use of the methiodide salt of this aldehyde. A mixture of 11.6 g. of the quaternary salt, 2.2 g. of 2,5-diketopiperazine, 4.0 g. of sodium acetate, and 12.0 g. of acetic anhydride was heated 3 hr. in an oil bath at 170°. The resulting insoluble product was washed with hot water and with hot methanol, then recrystallized twice from dimethylformamide. The tan crystals melted at 340°[3]; they formed an orange solution in acetic acid which became colorless on addition of a little concentrated HCl.

Anal. Calcd. for $C_{22}H_{24}N_4O_2$: C, 70.20; H, 6.41. Found: C, 69.98; H, 6.18.[4]

Walker 256 tumor screening test showed C/T 0.85 at 400 mg./kg.[5]; tissue culture screening test against KB cells *in vitro*: ED_{54}, 43 γ/ml.[6]

(1) This research was supported by a United States Public Health Service Grant CA-03717-5 from the National Cancer Institute.

(2) C. T. Bahner, J. Wilson, M. West, G. Browder, J. G. Goan, C. Cook, J. Fain, E. Franklin, and A. Myers, *J. Org. Chem.*, **22**, 683 (1957).

(3) Corrected for stem exposure; determined by use of Thiele tube.

(4) Average of two analyses by Weiler and Strauss, Oxford, England.

(5) We are grateful to Professor Alexander Haddow, Mr. J. E. Everett, and Mr. B. C. V. Mitchley of the Chester Beatty Research Institute for data on toxicity and activity against the Walker 256 tumor in rats weighing 200–250 g. Each compound was administered as a single i.p. injection in arachis oil on the day following tumor implantation or on the first day of the toxicity observation. Tumor bearing animals were sacrificed approximately 8 days later and the average weights of tumors in treated and untreated hosts reported as the ratio C/T.

(6) Results of the standard KB tumor cell inhibition tests carried out under sponsorship of the Cancer Chemotherapy National Service Center.

The Preparation of 4-Substituted Benzothiadiazines

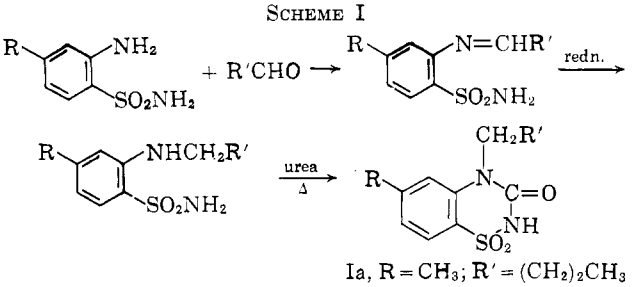
E. MAGNIEN,[1] W. TOM, AND W. OROSHNIK

U. S. Vitamin & Pharmaceutical Corporation, Yonkers, New York 10701

Received June 29, 1964

During our attempts to prepare cyclic analogs (I) of tolbutamide, a publication[2] appeared setting forth the synthesis of Ia. We have prepared Ia and twelve other 4-substituted analogs by an alternate route according to Scheme I.

SCHEME I



Ia, R = CH_3; R' = $(CH_2)_2CH_3$

In only one instance (**15**), when using 10% palladium on carbon in acetic acid solution, was catalytic reduction of a Schiff base successful. When the Schiff bases were refluxed in acetic acid with either di- or trimethylamine borane for 0.5 hr., pure reduction products were obtained in yields ranging from 84–99%. Schiff bases (**12–14**) prepared from *para*-substituted benzaldehydes did not give pure products by this procedure.

The 4-pyridylethyl compound (**21**) was prepared by addition of 4-vinylpyridine to *o*-aminobenzenesulfonamide. All cyclizations were carried out by heating the N-substituted sulfonamides with urea at 200–205°.[3] The N-pyridylethylsulfonamide was heated at lower temperatures (*ca.* 170°) since at 200° decomposition occurred with loss of 4-vinylpyridine.

Experimental[4]

Schiff Bases.—These were prepared by mixing equimolar amounts of the appropriate aniline and aldehyde in ethanol. The mixtures were allowed to stand from 7–24 hr. at room temperature, and the solvent was removed. Yields, analyses, recrystallization solvents, and melting points are indicated in Table I.

(1) Author to whom inquiries should be addressed.

(2) D. L. Simmons, J. M. Dodsworth, and F. L. Chubb, *Can. J. Chem.*, **41**, 804 (1963).

(3) D. V. Park and R. T. Williams, *J. Chem. Soc.*, 1760 (1950).

(4) Melting points were determined on Fisher-Johns block with a calibrated thermometer. Analyses were performed by Midwest Microlab, Inc.