and 0.62 g. of dibenzyl ketone 2,4-dinitrophenylhydrazone. Both compounds possessed no observable radioactivity.

Isotopic Assay.—For the determination of radioactivity, the sodium acetate was converted into *p*-nitrobenzyl acetate according to the direction of Bell and Reed.[2] The sodium phenylacetate was also converted into the free acid for combustion. All samples assayed were burned by a dry combustion method and converted to barium carbonate. The activity was counted at infinite thickness with a G-M. counter tube and compared with the count of a standard barium carbonate.

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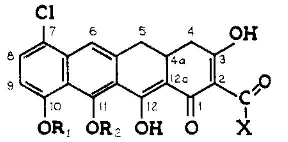
TAKATSUKI, OSAKA-FU, JAPAN

COMMUNICATIONS TO THE EDITOR

TOTAL SYNTHESIS OF TETRACYCLINES. I. (±)-DEDIMETHYLAMINO-12a-DEOXY-6-DEMETHYLANHYDROCHLOROTETRACYCLINE

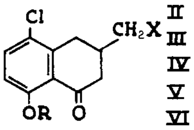
Sir:

Since the structure elucidation in 1952 of oxytetracycline[1] and of chlorotetracycline,[2] synthetic efforts have led to certain dicarbocyclic degradation products[3] and to model substances having structural similarities to portions of the tetracycline molecule. More recently Shemyakin[4] and Muxfeldt[5] have described the preparation of tricyclic intermediates suitable for further synthetic elaboration. We now report the total synthesis of biologically active (±)-dedimethylamino-12a-deoxy-6-demethylanhydrochlorotetracycline (I) and its comparison with a sample prepared from the natural antibiotic 6-demethylchlorotetracycline[6]



I $R_1=R_2=H$, $X=NH_2$

XII $R_1=CH_2C_6H_5$, $R_2=CH_3$, $X=OC_2H_5$



II $R=CH_3$, $X=CO_2H$

III $R=CH_3$, $X=COCl$

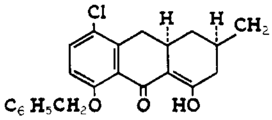
IV $R=CH_3$, $X=CHO$

V $R=H$ $X=CH(CH_2CO_2H)_2$

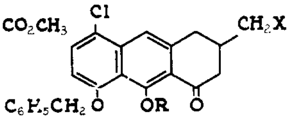
VI $R=CH_2C_6H_5$, $X=CH(CH_2CO_2CH_3)_2$

Alkylation of diethyl sodiomalonate with 2-chloro-5-methoxybenzyl bromide, prepared by peroxide-catalyzed bromination of 4-chloro-3-methylanisole with N-bromosuccinimide, gave the benzylmalonic ester (b.p. 147–155° (0.3 mm.); found: C, 57.38; H, 6.32). Reduction of the latter with lithium aluminum hydride produced the corresponding 1,3-diol, which was converted by standard methods to the bis-methanesulfonate (m.p. 75–77°; found: C, 40.59; H, 5.09) and thence to the dinitrile. Alkaline hydrolysis to the substituted benzylglutaric acid and subsequent ring closure with polyphosphoric acid produced the tetraloneacetic acid II (m.p. 193–196°; found: C, 57.69; H, 4.98).

Modified Rosenmund reduction of the acid chloride III gave 82% of the aldehyde IV (m.p. 89–91°; found: C, 61.63; H, 5.40). Piperidine-catalyzed condensation of IV with excess cyanoacetamide yielded a crystalline dicyanodiamide, which upon acid hydrolysis underwent demethylation to the phenolic diacid V (m.p. 181–182°; found: C, 56.45; H, 5.30). Reaction of V with benzyl chloride and subsequent esterification produced the diester VI (m.p. 62–63°; found: C, 65.10; H, 6.04). The latter was cyclized by sodium hydride in toluene to a crystalline tricyclic ester (m.p. 118–121°; found: C, 67.47; H, 5.58; Cl, 8.85; $\lambda_{max}^{CH_3OH}$ 343, 262, (225) mμ, log ϵ 4.19, 3.77, (4.31); $\lambda_{max}^{0.1\,N\,NaOH}$ 359, (260), 219 mμ, log ϵ 4.15, (3.92), 4.36) tentatively assigned relative stereochemistry VII on conformational grounds.



VII



VIII $R=H$, $X=CO_2CH_3$

IX $R=CH_3$, $X=CO_2CH_3$

X $R=CH_3$, $X=CO_2H$

XI $R=CH_3$, $X=COCH(CO_2C_2H_5)_2$

Angular bromination followed by dehydrobromination in collidine converted VII to the highly fluorescent phenol VIII, which was further transformed by the action of dimethyl sulfate and potassium carbonate into the methyl ether IX and thence to the tricyclic acid X (m.p. 176–177°; found: C, 67.72; H, 5.06; OCH_3, 7.27; λ_{max}^{MeOH} 377, 322, 309, 260 mμ, log ϵ 3.74, 3.53, 3.60, 4.55). Entry to the tetracyclic series was effected by converting acid X to the acylmalonate[7] XI, which was cyclized by sodium hydride in toluene to the ester XII[8] (m.p. 169–171°; found: C, 66.85; H, 5.08; OCH_3, 11.11; $\lambda_{max}^{MeOH(H+)}$ 390, 322, 266, 227, log ϵ 4.38, 4.02, 4.38, 4.49).

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[1] F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, THIS JOURNAL, **75**, 5455 (1953).

[2] (a) C. R. Stephens, L. H. Conover, R. Pasternack, F. A. Hochstein, W. T. Moreland, P. P. Regna, F. J. Pilgrim, K. J. Brunings and R. B. Woodward, *ibid.*, **74**, 4976 (1952); **76**, 3568 (1954); (b) C. W. Waller, B. L. Hutchings, R. W. Broschard, A. A. Goldman, C. F. Wolf and J. H. Williams, *ibid.*, **74**, 4981 (1952).

[3] (a) L. Conover, *ibid.*, **75**, 4017 (1953); (b) R. B. Woodward and E. F. Ullman, unpublished observations; E. F. Ullman, Ph.D. thesis, Harvard University, 1956; (c) Z. Horii, Y. Tamura and K. Tanaka, *Pharm. Bull.* (Tokyo), **5**, 284–285 (1957).

[4] M. M. Shemyakin, M. N. Kolosov, M. G. Karapetyan and E. S. Chaman, *Proc. Acad. Sci. U.S.S.R., Sect. Chem.*, **112**, 669 (1957).

[5] H. Muxfeldt, *Abhandlungen der Braunschweigischen Wissenschaftlichen Gesellschaft.*, **10**, 1 (1958).

[6] J. R. McCormick, N. O. Sjolander, U. Hirsch, E. R Jensen, A. P. Doerschuk, THIS JOURNAL, **79**, 4561 (1957).

[7] D. S. Tarbell and J. R. Price, *J. Org. Chem.*, **21**, 144 (1956); **22**, 245 (1957).

[8] Zinc dust distillation of the ester gave naphthacene.

Fusion of ester XII with ammonium formate[9] in a nitrogen atmosphere, and then dealkylation by hydrochloric acid in acetic acid gave (±)-amide I, as orange needles from dimethylformamide (dec. *ca.* 250°; $\lambda_{\max}^{\text{MeOH(H+)}}$ 433, 385, 330, 270 mμ, log ϵ 4.39, 4.19, 3.93, 4.44; $\lambda_{\max}^{\text{KBr}}$ 2.95, 6.33, 7.03, 8.06, 9.32 μ).

Natural 6-demethylchlorotetracycline was converted by known methods[2a] to dextrorotatory I (found: C, 59.15; H, 3.89; N, 3.87). Comparison with the synthetic amide by means of the characteristic infrared and ultraviolet spectra, bioassays and chromatographic behavior unambiguously demonstrated the chemical identity of the two samples.[10] Since the location of the 6-methyl group has been proven by degradation,[1,11] the present synthesis furnishes compelling support for the accepted framework of the tetracycline molecule.

[9] We are grateful to S. Kushner for valuable suggestions, including the use of this reagent.

[10] We are indebted to W. Fulmor and associates for the spectroscopic data, A. C. Dornbush and staff for microbiological assays, R. D. Mills for chromatographic work and L. Brancone and his staff for the microanalytical data cited herein.

[11] (a) J. S. Webb, R. W. Broschard, D. B. Cosulich, W. J. Stein and C. F. Wolf, THIS JOURNAL, **79**, 4563 (1957); (b) J. H. Boothe, A. Green, J. P. Petisi, R. G. Wilkinson and C. W. Waller, *ibid.*, **79**, 4564 (1957).

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RECEIVED JANUARY 20, 1959

CRYSTALLIZATION OF B_2O_3 AT HIGH PRESSURES[1]

Sir:

Solid B_2O_3 is commonly encountered as a glass, the preparation of the crystalline oxide being extremely difficult. By the conventional method of careful stepwise dehydration of H_3BO_3, microcrystals have been prepared.[2,3] Kracek, Morey and Merwin[3] were only able to prepare crystals having maximum dimensions of 0.05 mm. from experiments lasting eight months. Consequently, the only structural study[2] was based on powder diffraction data. In view of the possibility of incomplete dehydration which, for instance, had led to earlier erroneous conclusions,[4] attempts have been made to prepare by other methods single crystals for structural studies. This note describes the preparation of relatively large crystals of B_2O_3 by high pressure treatment of the powdered glass.

Pure B_2O_3 glass of >99% purity was obtained from the Pacific Coast Borax Company. No heavy metals were detected by spectroscopic analysis. Samples were contained in platinum or graphite capsules and subjected to pressures of 15,000 to 70,000 atmospheres at 300 to 600°. Rapid conversion to microcrystals was achieved in short periods. Thus, for example, at 600°, devitrification was complete after two minutes at 40,000 atmospheres. At pressures below about 20,000 atmospheres and 400°, the ordinary hexagonal crystals[2,3] were obtained (density = 2.46 g./cm.[3]). At higher pressures, a denser crystalline modification was found which has a density of 2.95 g./cm.[3] by sink-float method. The refractive indices and the X-ray powder diffraction data of the two forms are also widely different. Under optimum conditions, single crystals of both forms having dimensions up to 0.2 mm. have now been prepared. The dense crystals are only slowly attacked by water and dilute hydrofluoric acid. Preliminary experiments by high temperature X-ray diffraction showed that these may be heated slowly to above 500° with no observable transformation, the m.p. being about 510°. The m.p. of the ordinary B_2O_3 is reported to be 450 ± 2°.[3] Structural and related studies of single crystals of the two forms are now in progress.

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[2] S. V. Berger, *Acta Chem. Scand.*, **7**, 611 (1953).

[3] F. C. Kracek, G. W. Morey and H. E. Merwin, *Am. J. Sci.*, **35A**, 14 (1938).

[4] S. S. Cole and N. W. Taylor, *J. Am. Ceram. Soc.*, **18**, 55 (1935).

CRYSTALLINE POLY-(ALKYL ACRYLATES)

Sir:

Both free-radical[1,2] and anionic[1,3] stereospecific polymerization methods have been reported for the preparation of several types of crystallizable poly-(methyl methacrylate), and evidence concerning the structures of these polymers has been presented.[4] More recently, the preparation of crystalline poly-(*t*-butyl acrylate) was described by Miller and Rauhut.[5] The present communication reports the application of these stereospecific polymerization methods to a series of alkyl acrylates.

Poly-(isopropyl acrylate) has been synthesized in two different forms which crystallize in different, non-polymorphic structures possessing distinctly different infrared spectra. Unlike polymers of methyl methacrylate prepared by the same methods these polymers do not crystallize in a third structure on mixing. Type I poly-(isopropyl acrylate) is prepared at low temperature (< −70°) by photosensitized or cobalt-60 initiated free-radical polymerization in bulk or in toluene. For example, 30 g. of the monomer containing 0.12 g. of benzoin, degassed under vacuum and irradiated for 1.25 hours at −100° with a 60-watt ultraviolet source, yields 7.2 g. of polymer, $\overline{M}v$ 1.3×10^6. Crystallization may be effected readily by annealing or by solvent swelling techniques. X-Ray diffraction patterns of the crystalline material show strong scattering from spacings at 7.4 (vs); 4.35 (ms); and 4.25 (s) Å.

Poly-(isopropyl acrylate) of type II is prepared by anionic polymerization initiated by organo-

[1] T. G. Fox, *et al.*, THIS JOURNAL, **80**, 1768 (1958).

[2] T. G. Fox, *et al.*, *J. Polymer Sci.*, **31**, 173 (1958).

[3] R. G. J. Miller, *et al.*, *Chem. and Ind.*, 1323 (1958).

[4] J. D. Stroupe and R. E. Hughes, THIS JOURNAL, **80**, 2341 (1958).

[5] M. L. Miller and C. E. Rauhut, *ibid.*, **80**, 4115 (1958).