113–115°. One crystallization from ethyl acetate afforded analytically pure material, m.p. 121.5–122.0°.

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05. Found: C, 77.72; H, 8.13.

The N-*p*-nitrobenzoyl derivative of X melted at 188.0–188.5° after recrystallization from ethanol.

Anal. Calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48. Found: C, 68.82; H, 5.66.

Methylation of X.—To 0.40 g. of X in refluxing methanol was added slowly an equivalent amount of methyl iodide as a 2 millimolar solution in methanol. After the addition was complete, refluxing was continued for 0.25 hour. The oil remaining on evaporation of the methanol was taken up in 9 ml. of boiling acetone and then diluted with 15 ml. of water. On standing overnight in the cold, the solution deposited 130 mg. of crystalline IX, m.p. 145–148°. Recrystallization from aqueous acetone gave 80 mg. of material with m.p. 154–155°, which was not lowered on admixture with IX obtained as previously described.

α-Methyl-β-(2-piperidyl)-indole (XI).—2-Methylindole (0.63 g.) and 0.83 g. of Δ^1-piperideine trimer (dissolved in 10 ml. of 1 *N* hydrochloric acid) were allowed to condense in a fashion similar to that described for indole itself, except that 640 ml. of *p*H 7 phosphate buffer was used and the reaction was allowed to proceed for 60 hours. The brown, oily product obtained after basification and ether extraction was converted to the picrate, which was crystallized from 60% ethanol. Material thus obtained (0.4 g., 20%) gave an analysis which corresponded to the monohydrate; the m.p. of the picrate, although sharp, varied randomly between 135 and 175° on subsequent recrystallizations.

Anal. Calcd. for $C_{20}H_{21}N_5O_7 \cdot H_2O$: C, 52.06; H, 5.03. Found: C, 52.08; H, 5.18.

After being dried *in vacuo* (0.1 mm.) for 24 hours at 60°, the once-recrystallized picrate melted reliably at 175–177°. Through recrystallization and final vacuum drying, the melting point could be raised to 180–181°.

Anal. Calcd. for $C_{20}H_{21}N_5O_7$: C, 54.17; H, 4.77. Found: C, 54.15; H, 4.89.

α-Methyl-β-(2-pyridyl)-indole (XIII).—2-Pyridylacetone[9] (4.05 g.) was converted to its phenylhydrazone, which, after two recrystallizations from ligroin (b.p. 100–140°), melted at 121.5–123° and weighed 2.5 g. The rather unstable derivative (8.0 g.) was cyclized by refluxing in 100 ml. of concentrated hydrochloric acid for three hours. The reaction mixture was concentrated *in vacuo* to an oil, which, when treated with 20 ml. of 15% ammonium hydroxide, solidified. Extraction with ether and recrystallization of the recovered product from ligroin (100–140°)-ethyl acetate yielded 3.73 g. (50%) of α-methyl-β-(2-pyridyl)-indole, m.p. 134–136°. Two more recrystallizations raised the melting point to 137–138°.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81. Found: C, 80.56; H, 5.93.

Attempted cyclization of XII using gaseous hydrogen chloride and 95% ethanol resulted only in cleavage—phenylhydrazine was obtained as the hydrochloride.

Hydrogenation of XIII.—Sixty-two milligrams of XIII was hydrogenated over platinum in 95% ethanol to which had been added one equivalent of hydrogen chloride (calculated hydrogen uptake at room temperature and atmospheric pressure, 22.5 ml.; found 26.4 ml.). After removal of the catalyst by filtration and concentration of the filtrate *in vacuo*, aqueous alkali was added. Extraction with ether and subsequent evaporation left a reddish-brown oil which was dissolved in ether and converted to the picrate. One hundred and six milligrams (81%) of material which, after vacuum drying, melted at 175–177°, was obtained; recrystallization from 60% ethanol raised the melting point to 180°. A mixed melting point using picrate obtained by condensation of indole and Δ^1-piperideine was the same, and the infrared spectra of the bases regenerated from the picrates by alkali basification and chloroform extraction, were identical, as were the ultraviolet spectra of the same two substances.

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[9] J. P. Wibaut and M. G. J. Beets, *Rec. trav. chim.*, **59**, 553 (1940).

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

The Synthesis of DL-*cis*-3,5-*cis*-3′,5′-Tetramethyl-1,1′-spirobipiperidinium Bromide

BY C. R. NOLLER AND C. E. PANNELL

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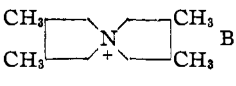
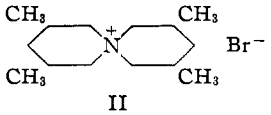
DL-*cis*-3,5-*cis*-3′,5′-Tetramethyl-1,1′-spirobipiperidinium bromide has been synthesized to provide an example of a compound having two like pair of enantiomorphic groups attached to a central atom.

Recently McCasland and Proskow[1] reported the preparation of *meso*-2,3-dimethyl-1,4-butanediol and the corresponding dibromide, and the condensation of the latter with pyrrolidine to give the spiro quaternary bromide. They stated that this work was done "to facilitate the solution of a more fundamental problem." We have learned by private communication with Dr. McCasland that their principal effort has been to synthesize the various stereoisomers of 3,3′,4,4′-tetramethyl-1,1′-spirobipyrrolidinium bromide (I).



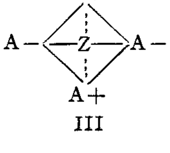
I



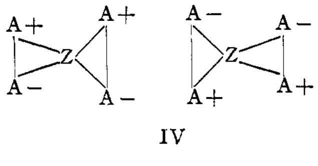
II

Inasmuch as we have synthesized the DL-*cis-cis* isomer of the analogous spirobipiperidinium compound II and have used procedures similar to those used by McCasland and Proskow, it seems desirable to report our results to date.

The particular isomer which we have synthesized is that in which the members of the pair of asymmetric carbon atoms in each ring are enantiomorphic and in which the pair in one ring is identical with the pair in the other. The molecule is an example of two like pair of enantiomorphic groups attached to a single atom Z. If no bond links the members of the enantiomorphic pair as in III, the molecule has a fourfold alternating (or mirror) axis of symmetry and is identical with its mirror image. If, however, the enantiomorphic groups are linked together to give a spiro structure, a pair of non-identical mirror images is



III



IV

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[1] G. E. McCasland and S. Proskow, THIS JOURNAL, **76**, 3486 (1954).

possible. This fact was pointed out first by Mohr[2] and independently, but much later, by Hearst.[3] The synthesis of compounds of this type is part of a series of attempts to prepare compounds in which a single atom is bonded to three asymmetric groups, two of which are enantiomorphic, or to two pair of enantiomorphic groups.[4]

The racemic form of stereoisomers of II having the configurations represented by IV was synthesized by the following series of reactions. 2,4-Dimethylglutaric acid was converted to the *meso*-anhydride[5] by the method of Bone and Perkin.[6] Reduction of the anhydride with lithium aluminum hydride gave *meso*-2,4-dimethyl-1,5-pentanediol in 88% yield. The latter compound was converted to the corresponding dibromide in 55% yield by means of phosphorus tribromide. Reaction of the dibromide with liquid ammonia[7] gave a 53% yield of the *dl-cis-cis* isomer of II. Attempts to resolve the spiro compound into its active components are now in progress.

Experimental

Ethyl 2,2,4-Pentanetricarboxylate.—To a solution of sodium ethoxide prepared from 37.8 g. (1.64 atoms) of sodium and 750 cc. of absolute alcohol was added 286 g. (1.64 moles) of ethyl methylmalonate. After cooling this solution to 40°, 330 g. (3.28 moles) of freshly distilled methyl methacrylate was added rapidly. Gentle refluxing occurred during the addition, and the solution was stirred at room temperature overnight. After distilling 500 cc. of alcohol, the residue was acidified with acetic acid, water added and the layers separated. The aqueous layer was extracted with ether, the extract combined with the ester layer, the ether removed, and the residue fractionated at reduced pressure. The recovered ethyl methylmalonate weighed 95 g.; the fraction b.p. 105–110° (1 mm.), weighed 208 g. (66% based on the malonate consumed), $n^{20}\text{D}$ 1.4341, d^{20}_4 1.044. A 30% yield of ester boiling at 250–285° has been reported[8] starting with ethyl methacrylate.

***meso*-α,γ-Dimethylglutaric Anhydride.**—A mixture of 50 g. (0.174 mole) of ethyl 2,2,4-pentanetricarboxylate and 125 cc. of 30% hydrochloric acid was refluxed for 16 hours, steam distilled to remove unchanged ester, and the residual aqueous solution allowed to stand at 5° overnight. After removal of the crystals, the addition of 25 cc. of concd. hydrochloric acid to the filtrate, followed by standing at 5° overnight, gave a further crop. The combined crops of crude product were dried in air, dissolved in 150 cc. of ether, the ether solution dried with sodium sulfate, and the ether distilled to reduce the volume to 30 cc. Addition of 20 cc. of benzene–ligroin (75–110°), 2:1 (vol.), gave 20.5 g. (74%) of the mixed α,γ-dimethylglutaric acids, m.p. 101–109°.

A solution of 15 g. (0.09 mole) of the dimethylglutaric acids in 75 cc. of acetic anhydride was refluxed for four hours, and the acetic acid and excess anhydride then removed by distillation. The residue was distilled at reduced pressure. The fraction boiling at 154–158° (20 mm.) solidified and was crystallized from a minimum amount of acetic anhydride and washed with cold ether to give 7.0 g. (52%) of odorless transparent crystals, m.p. 92–93°. The recorded melting point of the *meso*-anhydride is 93.5°.[6]

***meso*-2,4-Dimethyl-1,5-pentanediol.**—To 6 g. (0.15 mole) of lithium aluminum hydride under 100 cc. of absolute ether was added 10.2 g. (0.07 mole) of *meso*-α,γ-dimethylglutaric anhydride and then an additional 200 cc. of ether. The solution, protected from moisture, was stirred for four hours, and the excess hydride then destroyed with ethyl acetate. After the addition of 150 cc. of water and 50 cc. of concd. hydrochloric acid, the mixture was extracted in a continuous extractor with ether for eight hours. The ether extract was washed once with 10 cc. of water and dried over sodium sulfate. Removal of the ether and distillation at reduced pressure gave 8.4 g. (88.5%), b.p. 97–99° (2 mm.), $n^{20}\text{D}$ 1.4549, d^{20}_4 0.945.

Anal.[9] Calcd. for $C_7H_{16}O_2$: C, 63.59; H, 12.20. Found: C, 63.09; H, 12.33.

The α-naphthylurethan was prepared from the glycol and α-naphthyl isocyanate by heating the mixture on the steam-bath. After crystallizing the product from carbon tetrachloride–ligroin (75–110°) it melted at 128–129°.

Anal. Calcd. for $C_{29}H_{30}N_2O_4$: C, 74.02; H, 6.43; N, 5.95. Found: C, 73.45; H, 6.43; N, 6.11.

The ***p*-nitrobenzoate** prepared from the glycol and *p*-nitrobenzoyl chloride in pyridine melted after three crystallizations from ethyl alcohol at 114–114.5°.

Anal. Calcd. for $C_{21}H_{22}N_2O_8$: C, 58.60; H, 5.15; N, 6.51. Found: C, 58.59; H, 5.38; N, 6.59.

***meso*-1,5-Dibromo-2,4-dimethylpentane.**—To 7.4 g. (0.018 mole) of *meso*-2,4-dimethyl-1,5-pentanediol at 0° was added with stirring 10.2 g. (0.018 mole) of phosphorus tribromide over a period of 30 minutes, after which the temperature was allowed to rise to room temperature and stirring was continued for two hours. After an additional stirring for ten minutes on the steam-bath, the mixture was poured into water, the product extracted with benzene, and the extract washed five times with 3-cc. portions of cold concd. sulfuric acid. After thorough washing with water, the benzene solution was dried over anhydrous calcium sulfate. Removal of the benzene and distillation of the residue at reduced pressure gave 7.6 g. (53%), b.p. 72–73° (2 mm.), $n^{20}\text{D}$ 1.5042, d^{20}_4 1.550.

Anal. Calcd. for $C_7H_{14}Br_2$: C, 32.58; H, 5.47; Br, 61.95. Found: C, 32.55; H, 5.55; Br, 61.73.

***cis*-3,5-*cis*-3′,5′-Tetramethyl-1,1′-spirobipiperidinium Bromide.**—To 2.32 g. (0.0045 mole) of *meso*-1,5-dibromo-2,4-dimethylpentane in a Carius tube was added 13 cc. of liquid ammonia. The tube was sealed without disturbing the bottom layer of the dibromo compound and allowed to stand at room temperature for six days. After cooling and opening the tube, the ammonia was decanted and the residue extracted at room temperature with butanol. The extract was filtered to remove the ammonium bromide and the spirobipiperidinium bromide was precipitated by the addition of ether. Crystallization from 2-propanol gave 0.7 g. (53%) of white crystalline product, m.p. 298–299° dec.

Anal. Calcd. for $C_{14}H_{28}BrN$: C, 57.92; H, 9.70; Br, 27.53; N, 4.83. Found: C, 57.85; H, 9.38; Br, 27.10; N, 4.94.

STANFORD, CALIFORNIA

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(2) E. Mohr, *J. prakt. Chem.*, [2] **68**, 382 (1903).

(3) P. J. Hearst, Ph.D. Thesis, Stanford University, 1950, p. 11.

(4) D. Spencer, Master's Thesis, Stanford University, 1942; C. R. Noller, *Science*, **105**, 546 (1947); C. D. Heaton, Ph.D. Thesis, Stanford University, 1949; G. G. Lowry, Master's Thesis, Stanford University, 1951; M. J. Diamond, Ph.D. Thesis, Stanford University, 1952.

(5) *Cf.* E. Möller, *Ber.*, **43**, 3250 (1910); *Lunds Univ. Årsskr.*, **15**, 56 pp. (1919); *C. A.*, **14**, 942 (1920).

(6) W. A. Bone and W. H. Perkin, Jr., *J. Chem. Soc.*, **67**, 429 (1895).

(7) J. v. Braun, *Ber.*, **70**, 991 (1937).

(8) K. Auwers and E. Köbner, *ibid.*, **24**, 1936 (1891).

(9) Microanalyses by Microchemical Specialties Co., Berkeley 3, Calif.