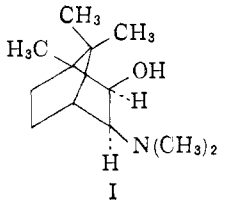

I

### Experimental[5]

*dl-exo*-**3-Dimethylaminoisoborneol** was prepared from *dl*-camphor. Camphorquinone (m.p. 196.5–197.5°) was produced in 86% yield by Riley oxidation[6] of camphor, converted to 3-methylaminocamphor (91% crude yield, purified *via* the perchlorate, m.p. 179–181°),[6] methylated to 3-dimethylaminocamphor (52% yield of pure perchlorate, m.p. 209–213°),[7] and then reduced in quantitative yield, to *dl-exo*-3-dimethylaminoisoborneol by catalytic hydrogenation in ethanol with Raney nickel catalyst,[6,7] at *ca.* 40 kg./cm.$^2$ The product separated from hexane as needles, m.p. 106.5–108°. Some batches required conversion to the perchlorate (m.p. 242–243° with sintering at 239°, after crystallization from ethanol–ether), followed by regeneration of the base, and crystallization to obtain pure *dl*-3-dimethylaminoisoborneol melting at 111–112°. Especially thorough drying was required to reach this melting point. Duden and Pritzkow[8] reported an isomer which melted at *ca.* 80°.

*Anal.* Calcd. for $C_{12}H_{23}NO$: C, 73.16; H, 11.77; N, 7.11. Found: C, 73.05; H, 11.80; N, 7.13.[9]

***dl*-3-Dimethylaminoisobornyl Acetate.**—A mixture of 5.0 g. (0.026 mole) of *dl*-3-dimethylaminoisoborneol with 200 ml. of acetic acid and 50 ml. of acetic anhydride was refluxed for 1 day and then the acid and anhydride were removed *in vacuo*. The residue was fractionated to give 4.4 g. of acetate, b.p. 72–73° (0.4 Torr.).

*Anal.* Calcd. for $C_{14}H_{25}NO_2$: C, 70.35; H, 10.58. Found: C, 70.05; H, 10 54.

The **hydrobromide** was prepared in propanol-2, and crystallized from propanol-2 and hexane as dull white needles, m.p. 239.5–242° with intumescence.

*Anal.* Calcd. for $C_{14}H_{25}NO_2 \cdot HBr$: C, 52.54; H, 8.19; N, 4.38. Found: C, 52.76; H, 8.64; N, 4.60, 4.37.

The **methobromide** was obtained by treatment of a methanolic solution of the base with methyl bromide at −30°, followed by allowing the mixture to reflux for several hours prior to removal of solvents. A creamy product resulted; it was necessary to crystallize the quaternary salt four times from propanol-2 and hexane to give pure white, fluffy needles, m.p. 183.5–185° with intumescence.

*Anal.* Calcd. for $C_{15}H_{28}BrNO_2$: C, 53.94; H, 8.45; N, 4.19. Found: C, 53.80; H, 8.72; N, 4.50.

***dl*-3-Dimethylaminoisobornyl Diphenylacetate.**—Excess diphenylacetic anhydride (30.0 g., made after the method of Hurd, *et al.*[10]) was added to a solution of 5.0 g. (0.026 mole) of 3-dimethylaminoisoborneol, and the mixture was refluxed for 36 hr. The benzene was removed and the residue dissolved in boiling ether. Chilling caused crystallization of the excess anhydride, which was removed, and then the filtrates were treated with hydrogen chloride. The **hydrochloride** separated slowly from methanol–ethyl acetate as prismatic crystals, m.p. 220–248° dec. A yield of 8.6 g. (79%) was obtained.

*Anal.* Calcd. for $C_{26}H_{33}NO_2 \cdot HCl$: C, 72.96; H, 8.01; N, 3.27. Found: C, 72.66; H, 8.14; N, 3.16.

The **base** was liberated from the hydrochloride and crystallized from methanol by addition of ethylene glycol. A cryptocrystalline solid resulted, m.p. 63–64°.

*Anal.* Calcd. for $C_{26}H_{33}NO_2$: C, 80.03; H, 8.50; N, 3.58. Found: C, 80.03; H, 9.01; N, 3.86.

The **methobromide** was made in methanol and crystallized, with some difficulty, from a 1:2:4 mixture of methanol, propanol-2, and hexane. The creamy product melted at 213–250° dec. and appeared to be a hemihydrate.

*Anal.* Calcd. for $C_{27}H_{36}BrNO_2 \cdot 0.5H_2O$: C, 65.51; H, 7.53; N, 2.83. Found: C, 65.56; H, 7.43; N, 2.85.

(5) All melting points were measured on a Fisher–Johns block. Analyses were carried out by Mr. J. Weinberger.

(6) H. Rupe and A. Tommasi di Vignano, *Helv. Chim. Acta*, **20**, 1078 (1937).

(7) H. Rupe and W. Flatt, *ibid.*, **14**, 1016 (1931).

(8) P. Duden and F. Pritzkow, *Ber.*, **32**, 1542 (1899).

(9) Basic nitrogen determination by the method of G. Toennies and T. P. Callan, *J. Biol. Chem.*, **125**, 259 (1938).

(10) C. D. Hurd, R. Christ, and C. L. Thomas, *J. Am. Chem. Soc.*, **55**, 2589 (1933).

## Aromatic Azo Acids as Possible Antineoplastic Compounds[1]

NORMAN RABJOHN AND J. F. PORTER

*Department of Chemistry, University of Missouri, Columbia, Missouri*

*Received July 18, 1963*

As a part of a program designed to synthesize azo and hydrazo fatty acids and derivatives as possible anticancer agents,[2] it appeared to be of interest to prepare some aromatic azo acids for comparative purposes. The carboxy substituted 4-alkyl- and 4,4′-dialkylazobenzenes described in Table I seemed to afford a simple approach to the desired structures. They were obtained by a conventional condensation of properly substituted aromatic amines with aromatic nitroso compounds, which were prepared by known synthetic procedures.

**Pharmacological Results.**—The data which are available to date indicate that the azo acids listed in Table I are inactive against Sarcoma 180, Lymphoid Leukemia L-1210, and Adenocarcinoma 755. The results were supplied by Dr. Joseph Leiter, Cancer Chemotherapy National Service Center, Bethesda, Maryland. Information in regard to test procedures may be located in publications from the National Service Center.[3]

### Experimental[4]

**Materials.**—Nitrosobenzene,[5] *p*-carboxy-,[6] *p*-ethyl-,[7] and *p*-methylnitrosobenzene[8] were prepared from the corresponding nitro compounds. *p*-Aminobenzoic acid was a commercial product, and *p*-aminophenylacetic acid was obtained by the ammonium polysulfide reduction of *p*-nitrophenylacetic acid.[9] *p*-Ethylaniline[10] was prepared from *p*-ethylacetophenone,[11] through the corresponding oxime,[12] which was rearranged by means of polyphosphoric acid to *p*-ethylacetanilide[13] which then was hydrolyzed by alkali to the desired amine. A similar series

(1) Supported in part through Grant CY-4662 from the Cancer Chemotherapy National Service Center, National Cancer Institute, U. S. Public Health Service.

(2) M. C. Chaco and N. Rabjohn, *J. Org. Chem.*, **27**, 2765 (1962).

(3) J. Leiter, A. R. Bourke, D. B. Fitzgerald, S. A. Schepartz, and I. Wodinsky, *Cancer Res.* (Supplement), **22**, 363 (1962).

(4) Melting points were taken in capillary tubes in a silicone oil bath and are corrected. Microanalyses by Drs. Weiler and Strauss, Oxford, England.

(5) G. H. Coleman, C. M. McCloskey, and F. A. Stuart, "Organic Syntheses," Coll. Vol. 3, John Wiley and Sons, New York, N. Y., 1955, p. 668.

(6) F. J. Alway, *Am. Chem. J.*, **32**, 385 (1904).

(7) Y. Tsudzuki, *Bull. Chem. Soc. Japan*, **17**, 102 (1942); *Chem. Abstr.*, **41**, 4463 (1947).

(8) E. Bamberger, *Ber.*, **28**, 245 (1895).

(9) G. R. Robertson, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, N. Y., 1932, p. 52.

(10) E. Schreiner, *J. prakt. Chem.*, **81**, 557 (1910).

(11) D. T. Mowry, M. Renoll, and W. F. Huber, *J. Am. Chem. Soc.*, **68**, 1105 (1946).

(12) A. Klages, *Ber.*, **35**, 2245 (1902).

(13) L. N. Nikolenko and K. K. Babievskiĭ, *Zh. Obshch. Khim.*, **25**, 2231 (1955); *Chem. Abstr.*, **50**, 9314 (1956).

TABLE I

AZO ACIDS, R—C6H4—N=N—C6H4—(CH2)nCO2H

| Compound R | n | Reagents p-H2NC6H4- | Reagents p-NOC6H4- | M.p., °C. | Formula | Analyses, % Calcd. C | Calcd. H | Found C | Found H | Ultraviolet absorption λmax, mμ (ε × 10⁻³) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | 0 | $CO_2H$ | H | 247–249 | $C_{13}H_{10}N_2O_2$[a] | . . . | . . . | . . . | . . . | 228 (112) | 320 (212) | 434 (10) |
| H | 1 | $CH_2CO_2H$ | H | 193–195 | $C_{14}H_{12}N_2O_2$ | 69.99 | 5.03 | 70.30 | 5.22 | 230 (123) | 320 (202) | 434 (5.9) |
| $CH_3$ | 0 | $CO_2H$ | $CH_3$ | 280–282 | $C_{14}H_{12}N_2O_2$ | 69.99 | 5.03 | 70.13 | 5.25 | 231 (117) | 331 (258) | 440 (8.8) |
| $CH_3$ | 1 | $CH_2CO_2H$ | $CH_3$ | 217–219 | $C_{15}H_{14}N_2O_2$ | 70.85 | 5.55 | 70.60 | 5.35 | 234 (139) | 327 (238) | 434 (8.3) |
| $C_2H_5$ | 0 | $C_2H_5$ | $CO_2H$ | 245–247 | $C_{15}H_{14}N_2O_2$ | 70.85 | 5.55 | 70.97 | 5.74 | 229 (114) | 330 (247) | 441 (8.9) |
| $C_2H_5$ | 1 | $CH_2CO_2H$ | $C_2H_5$ | 193–195 | $C_{16}H_{16}N_2O_2$ | 71.62 | 6.01 | 71.83 | 6.43 | 234 (127) | 327 (194) | 435 (10) |
| $n$-$C_3H_7$ | 0 | $n$-$C_3H_7$ | $CO_2H$ | 232–234 | $C_{16}H_{16}N_2O_2$ | 71.62 | 6.01 | 71.64 | 6.18 | 231 (113) | 330 (264) | 443 (8.4) |

[a] Spectra measured in 95% ethanol on a Beckman DB spectrophotometer. [b] H. D. Anspon, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, New York, N. Y., 1955, p. 711.

of reactions was used to transform *n*-propylbenzene to *n*-propylaniline.[14]

***p*-Phenylazophenylacetic Acid.**—The following procedure is representative of those used to synthesize the azo acids recorded in Table I.

To a hot solution of 25 g. (0.17 mole) of *p*-aminophenylacetic acid in 165 ml. of glacial acetic acid was added 17.8 g. (0.17 mole) of nitrosobenzene. The reaction mixture was allowed to stand at room temperature for 20 hr. and the precipitate which had formed was collected by filtration, washed with acetic acid, and then with water. After two recrystallizations from 95% ethanol (400 ml.), there was obtained 20.6 g. (52%) of product, m.p. 193–195°.

(14) Ng. Ph. Buu-Hoï, Ng. D. Xuong, and Ng. H. Nam, *J. Chem. Soc.*, 1573 (1955).

## Some Derivatives of 2,2′-(Phenylimino)diethanol

ALEX COHEN AND R. STUART TIPSON

*National Bureau of Standards, Washington 25, D. C.*

*Received April 24, 1963*

Because N,N-bis(2-chloroethyl)aniline (I) and 1,4-butanediol dimethanesulfonate (II) are carcinostats,[1,2] it was deemed desirable to prepare and study a new compound possessing structural features of both I and II, namely, the dimethanesulfonate (III) of 2,2′-(phenylimino)diethanol (IV). Compound III might be expected to exhibit behavior somewhat analogous to that of I, because a methylsulfonyloxy group resembles a halogen atom in some of its chemical properties.[3] Indeed, its carcinostatic activity might even prove higher than that of I because, whereas the *p*-aldehyde derived from I is inactive, that related to III is active.[4]

Interestingly, although the dibenzenesulfonate (V),[5,6] di-*p*-toluenesulfonate (VI),[5,6] and bis-*p*-nitrobenzenesulfonate[7] of IV have been prepared, III does not appear to have been described, despite the preparation[5] of the dimethanesulfonate of 2,2′-(2,4-dinitrophenylimino)-diethanol.

In 1951, IV (in pyridine) was treated with benzenesulfonyl chloride, and a 26% yield of recrystallized V was isolated[5]; similarly, a 35% yield of pure VI was obtained.[5] In the following year, an "improvement" was patented,[6] in which IV was converted to its disodium derivative and this, in xylene, was treated with *p*-toluenesulfonyl chloride to afford pure VI in an even poorer yield (16.3%). Consequently, we first attempted the preparation of III by a route different from either of these, namely, by the reaction of I with two molecular proportions of silver methanesulfonate in acetonitrile. Compound III was isolated, in quantitative yield, as a sirup which was readily converted into its crystalline hydrochloride. For the preparation of I from IV, an improved method, based on that devised[8] for the direct synthesis of N-(2-chloroethyl)aniline hydrochloride from 2-anilinoethanol, was developed; this gave the crystalline hydrochloride of I directly. The preparation and properties of this salt are described here because, although it has been used in pharmacological and hydrolysis studies,[9] its properties have never, so far as can be ascertained, been reported in the literature.

Although III was successfully prepared in this way, the method is slow and tedious; moreover, it involves the prior preparation of both I and silver methanesulfonate. We therefore attempted the synthesis of III directly from IV, by rapid sulfonylation[10]; this gave a quantitative yield of III, isolated as its crystalline hydrochloride. A modification of the procedure afforded pure V and VI in yields of 87 and 90%, respectively, as compared with reported yields[5] of 26 and 35%.

Such compounds as III can undergo intramolecular transformation. Hence, in order to verify the structure of III, the compound was converted into the corresponding *p*-aldehyde (VII). This was identical with a specimen of *p*-{bis[2-(methylsulfonyl)-oxyethyl]-amino}benzaldehyde prepared[4] from *p*-[bis(2-chloroethyl)amino]benzaldehyde (VIII), showing that III had the proposed structure.

(1) A. Haddow, G. A. R. Kon, and W. C. J. Ross, *Nature*, **162**, 824 (1948); A. Haddow and G. M. Timmis, *Acta Unio Intern. Contra Cancrum*, **7**, 469 (1951).

(2) A. Loveless and W. C. J. Ross, *Nature*, **166**, 1113 (1950).

(3) R. S. Tipson, *Advan. Carbohydrate Chem.*, **8**, 107 (1953).

(4) R. C. Elderfield, R. N. Prasad, and T.-K. Liao, *J. Org. Chem.*, **27**, 573 (1962).

(5) G. M. Timmis, British Patent 662,645 (1951).

(6) G. M. Timmis, British Patent 672,691 (1952).

(7) M. Ishidate, Y. Sakurai, and S. Owari, *Pharm. Bull.* (Tokyo), **5**, 203 (1957).

(8) R. S. Tipson, *J. Org. Chem.*, **27**, 1449 (1962).

(9) C. C. Hunt, *J. Pharmacol. Exptl. Therap.*, **95**, 177 (1949); L. F. Larionov, *Brit. J. Cancer*, **10**, 26 (1956); V. M. Rakova, A. D. Chinaeva, and A. Y. Berlin, *J. Gen. Chem. USSR*, **29**, 3922 (1959); compare, "The Merck Index," 7th Ed., P. G. Stecher, Ed., Merck & Co., Inc., Rahway, N. J., 1960, p. 622.

(10) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).