(4) H. H. Otto, *Pharm. Zentralhalle*, **107**, 444 (1968).
(5) L. Bernardi, R. DeCastiglione, and U. Scarponi, *J. Chem. Soc., Chem. Commun.*, 320 (1975).
(6) (a) K. Hirai, H. Matsuda, and Y. Kishida, *Chem. Pharm. Bull.*, **21**, 1305 (1973); (b) A. K. Bose, B. Dayal, J. C. Kapur, B. Lal, and M. S. Manhas, *Tetrahedron Lett.*, 3135 (1974).
(7) S. Kukolja, *J. Am. Chem. Soc.*, **93**, 6267 (1971).
(8) F. G. Bordwell and B. M. Pitt, *J. Am. Chem. Soc.*, **77**, 572 (1955).
(9) D. L. Tuleen and T. B. Stephens, *Chem. Ind. (London)*, 1555 (1966).
(10) D. L. Tuleen and V. C. Marcum, *J. Org. Chem.*, **32**, 204 (1967).

Regiospecific Synthesis of Isogabaculine

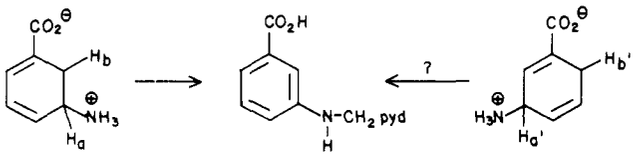
Samuel Danishefsky* and Fred M. Hershenson[1]

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received September 19, 1978

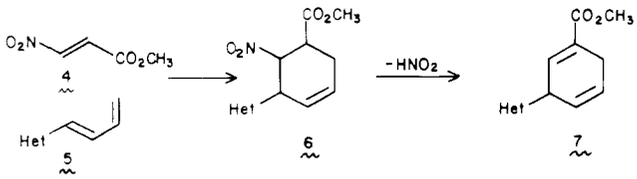
Recently, Mishima and co-workers reported the isolation of the amino acid gabaculine (1) from *Streptomyces toyocaensis*.[2] This curious compound, discovered in the course of studies on enzyme inhibitors, exhibited activity against γ-aminobutyrate aminotransferase (GABA-T).

Rando has set forth an interesting proposal wherein the activity of 1 arises from its competitive reaction with pyridoxal phosphate. It is felt that Schiff base formation is followed by irreversible conversion to *N*-(*m*-carboxyphenyl)pyridoxamine phosphate.[3] Presumably, the generation of **2** involves the usual Schiff base condensation from 1 + pyridoxal phosphate, followed by tautomerizations of H_a and H_b, successively. In the light of these conderations, it would be of interest to examine the behavior of compound **3** with pyridoxal phosphate. It will be recognized that hydrogens a′ and b′ in compound **3** are related in an allylic sense to hydrogens a and b in **1**.

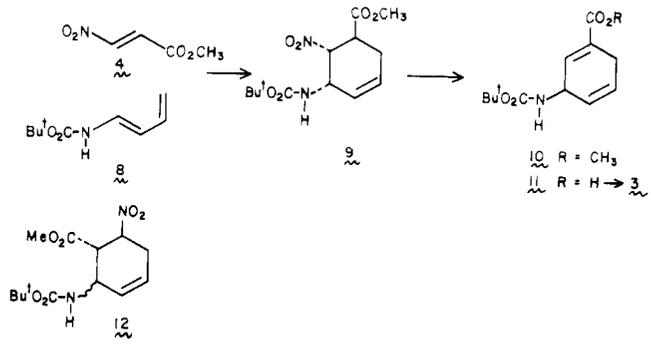


1 2 pyd = pyridoxyl 3

Syntheses of gabaculine have been described by Mishima[2] and subsequently by Sharpless.[4] We have been concerned with developing general routes to dihydrobenzenes containing heteroatoms at one of the sp^3 carbons.[5] Our approach, summarized below, involves Diels–Alder reactions of methyl β-nitroacrylate (**4**),[6] which achieve substitution patterns not accessible via the more precedented use of propiolate esters. It seemed attractive to apply this method to a synthesis of compound **3**, which we have termed "isogabaculine". An efficient regiospecific synthesis of **3** is described below.



Cycloaddition of the recently described 1-(*N*-acylamino)-1,3-diene **8**[7] with nitroacrylate **4** provided the Diels–Alder adduct **9**, which crystallized directly from the reaction medium in 68% yield. Examination of the mother liquors of the cycloaddition reaction indicated **9** to be the principal component. Chromatography of the mother liquors on silica gel afforded first, traces of an oily regioisomer of **9** whose NMR spectrum [δ 3.36 ($C\underline{H}CO_2Me$, dd, J = 12 and 6 Hz] indicated it to be structure **12**. In pure form only ca. 0.5% of **12** was obtained, though in fact, there may well have been as much as 1% present in the crude reaction mixture. There was next eluted additional traces of an apparent stereoisomer of **9**, though this was not obtained in pure form. The next fractions contained additional quantities of **9**. However, for preparative ease, the mother liquors were in fact not processed in the synthesis.



The stereochemistry of **9** can not be defined with certainty. It would appear that the *E* relationship of the carbomethoxy and nitro groups of **4** gives rise to a trans relationship of these groups in **9**. Indeed, the coupling constant between the "nitro" and "carbomethoxy" methine protons is 12 Hz. The coupling constant between the "nitro" and "urethane" methine protons is 5 Hz. This would tend to suggest the arrangement shown in **9**, wherein the carbomethoxy and nitro groups are equatorial while the urethane is quasi-axial. However, this assignment is not definitive since the stereoisomer of **9** could not be obtained in sufficiently pure form for meaningful NMR analysis. In any case, in keeping with earlier findings,[5] essentially complete regiochemical control was exerted by the nitro group.

Treatment of **9** with 1 equiv of diazobicycloundecene (DBU) furnished the dihydrobenzene derivative **10** in 70% yield. Conversion of **10** into "isogabaculine" (**3**) was accomplished in two steps. Hydrolysis of the ester with aqueous NaOH followed by acidification and immediate extraction with methylene chloride afforded the intermediate carbamate acid **11** in 73% yield. Treatment of **11** with a 10% aqueous HCl solution and passage of the resultant acidic solution through an ion-retardant ion resin (Bio-Rod AG 11A8), followed by lyophilization of the appropriate fractions, gave *dl*-isogabaculine (**3**) as a white powder in 55% yield. Investigation of the biological properties of **3** is planned.

Experimental Section[8]

Diels–Alder Reaction of Methyl Nitroacrylate (4) with *tert*-Butyl *trans*-1,3-Butadiene-1-carbamate (8). Formation of Methyl 5-(*N*-*tert*-Butoxycarbonylamino)-6-nitro-3-cyclohexene-1-carboxylate (9). A solution of 1.250 g (9.5 mmol) of nitroacrylate[6] **4** in benzene (3.5 mL) was added in dropwise portions over a 5-min period to a stirred solution of carbamate **8**[7] (1.613 g, 9.5 mmol) in benzene (6.5 mL) at room temperature. After stirring for 3 h at room temperature, the reaction mixture was filtered and the solid that was obtained was washed once with benzene (5 mL) to furnish **9** (1.934 g, 68%) as a colorless, analytically pure solid: mp 166–168 °C; λ_{max} ($CHCl_3$) 2.94, 5.77, 5.81, 6.41, 7.32 μm; δ (Me_2SO-d_6, 250 MHz) 1.36 (9 H, s, *tert*-butyl), 2.05–2.13 and 2.44–2.56 (2 H, m, allylic CH_2), 2.50–3.60 (1 H, m, R_2CHCO_2Me), 3.65 (3 H, s, OCH_3), 4.78–4.86 (1 H, m, R_2CHNCO_2), 5.10 (1 H, d of d, J = 12 and 5 Hz, R_2CHNO_2), 5.62–5.67 and 5.77–5.82 (2 H, m, olefinic), 7.25 (1 H, d, J = 9.7 Hz, NH).

Anal. Calcd for $C_{13}H_{20}N_2O_6$: C, 51.99; H, 6.71; N, 9.33. Found: C, 52.31; H, 6.74; N, 9.20.

Methyl 5-(*tert*-Butoxycarbonylamino)-2,5-dihydrobenzoate (10). A cooled (5 °C) solution of **9** (1.503 g, 5.0 mmol) in THF (20 mL) was treated with a solution of DBU (0.767 g, 5.0 mmol) in THF (5 mL) to form a yellow solution. A colorless precipitate began to form after 15 min. The reaction mixture was stirred for 6 h, during which time the temperature was gradually allowed to return to room temperature. The reaction mixture was poured into water (25 mL) and then ex-

0022-3263/79/1944-1180$01.00/0

tracted with methylene chloride (4 × 15 mL). The combined organic extracts were washed with brine (2 × 75 mL), dried, and evaporated to dryness. Trituration of the solid residue with hexane (15 mL) followed by filtration and further washing with hexane (2 × 5 mL) provided 0.887 g (70%) of **10** as a colorless solid: mp 122–127.5 °C; λ_{max} ($CHCl_3$) 2.93, 5.83 μm; δ ($CDCl_3$) 1.42, (9 H, s, *tert*-butyl), 2.70–2.90 (2 H, m, allylic CH_2), 3.71 (3 H, s, OCH_3), 4.40–4.85 (2 H, m, R_2CHNCO_2 and NH), 5.50–5.95 (2 H, m, olefinic), 6.80 (1 H, br s, olefinic). Recrystallization of **10** from cyclohexane provided a colorless solid, mp 134–136 °C, with identical spectral properties as the material melting from 122 to 127.5 °C.[9]

5-(*tert*-Butoxycarbonylamino)-2,5-dihydrobenzoic Acid (11). A mixture of dihydrobenzoate **10** (0.177 g, 0.7 mmol) in 0.175 M NaOH solution (6.0 mL, 1.05 mmol) was stirred and heated to 55 °C for 6 h. The resultant yellow solution containing a trace of suspended solid was cooled to room temperature and filtered, and the filtrate was acidified with concentrated HCl (10 drops). The gelatinous mixture that formed was extracted with methylene chloride (4 × 5 mL), and the combined organic extract was then washed with brine (7 mL). After drying the organic layer and removal of the solvent by evaporation in vacuo, **11** was isolated as a colorless solid (0.122 g, 73%): mp 171–172 °C dec; λ_{max} ($CHCl_3$) 2.93, 3.1–3.3 (broad shoulder), 5.85 μm; δ ($CDCl_3$) 1.48 (9 H, s, *tert*-butyl), 2.80–3.00 (2 H, m, allylic CH_2), 4.55–5.15 (2 H, m, R_2CHNCO_2), 5.67–6.15 (2 H, m, olefinic), 7.10 (1 H, br s, olefinic).

Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 59.85; H, 6.97; N, 5.70.

Isogabaculine (3). A suspension of **11** (0.100 g, 0.4 mmol) in 0.1 N HCl (5 mL, 0.5 mmol) was stirred at 55 °C for 24 h. The mixture was cooled to room temperature and placed on a 1 × 20 cm column of Bio-Rod AG 11A8 ion retardation resin which had been previously washed with 600 mL of distilled water. The column was then eluted with distilled water, and the eluants were collected in 2-mL fractions. TLC (75% EtOH–25% H_2O–trace NH_4OH; ninhydrin spray/Δ) was used to monitor which fractions contained the amino acid (R_f 0.5). All of the product was removed from the resin in the first 20 mL of eluant. These fractions were combined and lyophilized to yield **3** as a colorless solid (0.0305 g, 55%): mp >280 °C; *m/e* 139 (P), 122, 105, 94 (base peak); δ (D_2O) −1.92 to −1.68 (2 H, m, allylic CH_2), −0.75 to −0.40 (1 H, m, R_2CHN), 0.92–1.48 (2 H, m, olefinic), 1.72–1.92 (1 H, m, olefinic).

Acknowledgments. This research was supported by a grant from the G. D. Searle Co. to F.M.H. to spend his sabbatical at the University of Pittsburgh. Additional support was also available through AI 13939-02. NMR spectra at 250 MHz were obtained on instrumentation supported by RR 00296-08.

Registry No.—**3**, 68582-58-1; **4**, 52745-92-3; **8**, 65899-50-5; **9**, 68582-59-2; **10**, 68582-60-5; **11**, 68582-61-6; **12**, 68582-62-7.

References and Notes

(1) Visiting Professor, University of Pittsburgh, 1978. Present address: G. D. Searle & Co., Chicago, Ill.
(2) K. Kobayashi, S. Miyazawa, A. Terahara, H. Mishima, and H. Kurihara, *Tetrahedron Lett.*, 537 (1976).
(3) R. R. Rando and F. W. Bangerter, *J. Am. Chem. Soc.*, **99**, 5141 (1977).
(4) S. P. Singer and F. B. Sharpless, *J. Org. Chem.*, **43**, 1448 (1978).
(5) S. Danishefsky, M. P. Prisbylla, and S. Hiner, *J. Am. Chem. Soc.*, **100**, 2918 (1978).
(6) Cf. J. E. McMurry and J. H. Musser, *Org. Synth.*, **56**, 65 (1977).
(7) L. E. Overman, G. F. Taylor, C. B. Petty, and P. J. Jessup, *J. Org. Chem.*, **43**, 2164 (1978).
(8) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded in chloroform solution using sodium chloride optics on a Perkin-Elmer 137 infrared spectrophotometer. The polystyrene absorption at 6.238 μm was used as a reference, and only selected high intensity absorptions are reported. The NMR spectra were measured in either $CDCl_3$ or $(CD_3)_2SO$ using tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ) relating to Me_4Si. The NMR spectrum of "isogabaculine" (**3**) was obtained from a D_2O solution of **3**, where the HDO singlet served as the internal standard (δ = 0.0). Mass spectra were determined on an LKB-9000 system by direct insertion. TLC was carried out using Merck precoated silica gel 60 F-254 plates, 0.25-mm thickness. All reactions were carried out under a nitrogen atmosphere. Organic extracts of reactions were dried over anhydrous magnesium sulfate, and solvents were removed under water aspirator pressure on a roto-vac (bath temperature <30 °C). Elemental microanalyses were performed by the Searle Laboratories Microanalytical Department.
(9) Combustion analyses of **10** repeatedly gave low (0.67–1.87%) values for C, while the found values for H and N were always within ±0.3%. In all samples, the NMR spectra were consistent with **10** and failed to exhibit the presence of impurities which would have caused the low carbon values.

Oxidation of Poly(nitro)anilines to Poly(nitro)benzenes. Synthesis of Hexanitrobenzene and Pentanitrobenzene

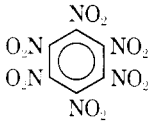
Arnold T. Nielsen,* Ronald L. Atkins, and William P. Norris

Chemistry Division, Research Department, Code 385, Naval Weapons Center, China Lake, California 93555

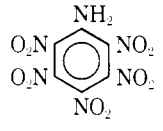
Received September 26, 1978

A new oxidation procedure has been developed suitable for conversion of poly(nitro)anilines to poly(nitro)benzenes (including those containing four or more nitro groups). Previously reported methods have been limited to the synthesis of trinitrobenzenes[1a,b] and a tetranitrotoluene.[1c]

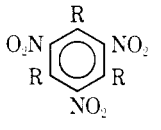
Hexanitrobenzene (**1**) has been prepared by oxidation of pentanitroaniline (**2**) by peroxydisulfuric acid (hydrogen peroxide in sulfuric acid solution at 25 °C). The material is a powerful explosive.



1



2

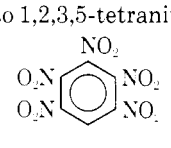


3a, R = C_6H_5O
b, R = CH_3O
c, R = NHOH
d, R = OH
e, R = NH_2

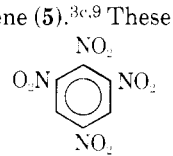
An account of the attempted preparation of **1** from trisubstituted derivatives of 1,3,5-trinitrobenzene (**3a**, R = C_6H_5O; **3b**, R = CH_3O) has been published.[2] Reaction of **3a,b** with hydroxylamine failed to yield the tris(hydroxylamino) derivative **3c**, a desired precursor to **1**. The oxidation of **3c** (said to be prepared by nitration of 1,3,5-tris(hydroxylamino)benzene) has been reported (without details) to yield **1**.[3] Our attempts to employ these synthetic routes were unsuccessful. The single crystal structure of **1** determined by X-ray crystallography was reported in 1966 without describing or referring to a method of synthesis.[4] No publication has yet appeared concerning the preparation of **1**.

Chemically, **1** resembles pentanitroaniline (**2**).[5] Reaction of **1** with aqueous sodium hydroxide solution (75 °C, 25 min), followed by acidification and conventional workup, gave 2,4,6-trinitrophloroglucinol (**3d**, 99%). Treatment of **1** in benzene solution with excess ammonia gave 1,3,5-triamino-2,4,6-trinitrobenzene (**3e**, 95%).

Our new procedure has been extended to oxidation of 2,3,4,6-tetranitroaniline[7,8] to pentanitrobenzene (**4**) and picramide to 1,2,3,5-tetranitrobenzene (**5**).[3c,9] These products,



4



5

the latter soluble in the reaction mixture, were isolated in 80–90% yields by filtration and/or extraction with methylene chloride followed by recrystallization from chloroform.

Hexanitrobenzene belongs to a small group of substances, $C_x(NO_2)_y$, for which we propose the name nitrocarbons (zero-hydrogen compounds composed only of nitro groups attached to carbon). The only such materials known are tetranitromethane and hexanitroethane. A preparation of tetranitroethylene which has been reported[10] could not be repeated.

Experimental Section

WARNING! All compounds described are powerful explosives and should be handled with great care.

Hexanitrobenzene (1). Pentanitroaniline[5] (**2**, 1.0 g) was dissolved