Notes

3-(Dialkylamino)methyladamantane-1-carboxylic Acids

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Received April 29, 1968

Substitution of the adamantyl group in a number of physiologically active compounds has resulted in enhanced activity; this was especially shown by Gerzon and his collaborators in a series of papers.[1] On the other hand, the antiviral activity of 1-aminoadamantane was the result of an intensive screening program on adamantane derivatives.[2] In connection with a study of tertiary aliphatic amines, we planned the synthesis and pharmacological evaluation of some 3-(dialkylamino)methyladamantane-1-carboxylic acids (**4a–d**).

Chemistry.—The 1-(dialkylamino)methyladamantanes (**3a–d**) would be appropriate starting materials for the preparation of the corresponding carboxylic acids **4.** Actually, the transformation of the adamantane-1-carboxylic acid (**1**) into the corresponding amides **2** and the reduction of these amides to the (dialkylamino)methyl derivatives **3** by $LiAlH_4$ proceed in excellent yields (Tables I and II).

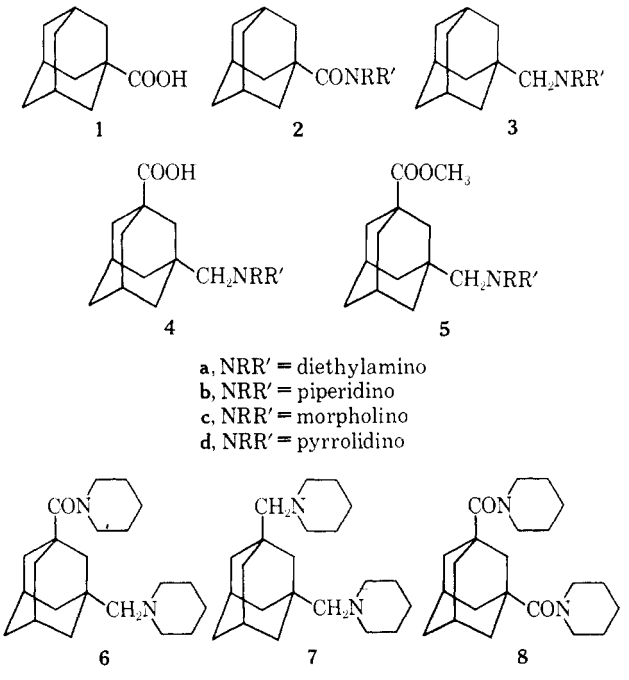

Table I

Adamantane-1-carboxamides (2)

Compd	NRR'	Yield, %	Mp, °C[a]	Formula[b]
2a	Diethylamino	92	64–67[c]	$C_{15}H_{25}NO$
2b	Piperidino	90	93–96	$C_{16}H_{25}NO$
2c	Morpholino	72	119–121	$C_{15}H_{23}NO_2$
2d	Pyrrolidino	88	108–110	$C_{15}H_{23}NO$

[a] After recrystallization from MeOH–H_2O, except for **2a**, which was recrystallized from EtOH–H_2O. [b] All compounds were analyzed for C, H, N. [c] E. I. duPont de Nemours & Co., [Netherlands Patent Appl. 6,408,505 (1965); *Chem. Abstr.*, **63**, 516 (1965)] reported mp 62–63°.

Table II

1-(N,N-Dialkylamino)methyladamantanes (3)

Compd	NRR'	Yield, %	Mp, °C	Formula	Picrate[a] mp, °C dec[b]
3a	Diethylamino	94	Oil	$C_{15}H_{27}N$[c]	174–176
3b	Piperidino	95	Oil	$C_{16}H_{27}N$	200
3c	Morpholino	97	60–64[d]	$C_{15}H_{25}NO$	236–238
3d	Pyrrolidino	96	Oil	$C_{15}H_{25}N$	178–180

[a] All picrates were analyzed for C, H, N. [b] After recrystallization from absolute EtOH. [c] This amine has been reported as the hydrochloride, mp 240–241°, in footnote *c* in Table I. [d] After recrystallization from EtOH, the free amine had mp 61–64° (analyzed for C, H, N); the corresponding hydrochloride had mp 308° dec after recrystallization from absolute EtOH–anhydrous Et_2O (analyzed for C, H, Cl, N).

The introduction of the carboxyl group into a tertiary carbon of **3** was tried by the Koch–Haaf carboxylation reaction,[3] which uses the *in situ* generation of CO from HCOOH in H_2SO_4 and the *t*-butyl cation generated from *t*-butyl alcohol. It is noteworthy that the method fails to introduce a second carboxyl group into adamantane-1-carboxylic acid.[3] In agreement with this observation no 1,3-disubstituted acid derivative was obtained starting with a carboxamide **2**. However, when this reaction was applied to the tertiary amines **3**, compounds of high melting point were obtained in yields ranging from 10 to 20%, while the initial amines were recovered in a proportion of 40–60% (Table III). The low yields of the reaction may be ascribed to the electron-withdrawing inductive effect of the ammonium nitrogen atom (Ad-CH_2N^+HRR'), which suppresses the generation of a tertiary carbonium ion on the adamantane moiety.

The derivatives thus obtained readily form hydrochloride salts, whose analyses agree with structure **4**. The presence of the carboxyl group was confirmed by esterification with diazomethane. A molecular weight determination of the picrate salt of the ester **5b** was in agreement with this formula. The introduction of the carboxyl group in a bridgehead position was proved unambiguously by transformation of the amino acid **4b** to the diamine **7**, *via* the amine–amide **6**. This diamine

(1) For the last paper of this series, see K. Gerzon, D. J. Tobias, Sr., R. E. Holmes, R. E. Rathbun, and R. W. Kattau, *J. Med. Chem.*, **10**, 603 (1967).

(2) For a review on this subject, see C. Runti, *Farmaco, Ed. Sci.*, **22**, 953 (1967).

(3) H. Koch and W. Haaf, *Angew. Chem.*, **72**, 628 (1960).

TABLE III

3-(N,N-DIALKYLAMINO)METHYLADAMANTANE-1-CARBOXYLIC ACIDS (4)

Compd	NRR'	Mp, °C	Recd initial amine 3, %	Yield, %	HCl[a] mp, °C dec[b]	Formula
4a	Diethylamino	130–140	60	12	244	$C_{16}H_{28}ClNO_2$
4b	Piperidino	129–131	40	22	270	$C_{17}H_{28}ClNO_2$
4c	Morpholino	175–180	53	11	260	$C_{16}H_{26}ClNO_3$
4d	Pyrrolidino	Oil	60	10	280	$C_{16}H_{26}ClNO_2$

[a] All hydrochlorides were analyzed for C, H, Cl, N. [b] After recrystallization from absolute EtOH or absolute EtOH–anhydrous Et_2O.

was found identical with the one obtained by $LiAlH_4$ reduction of the known 1,3-dipiperidide **8**.

The nmr spectrum of the ester **5a** shows typical features of a 1,3-disubstituted adamantane. Furthermore, the additivity relationship of chemical shifts, based on the shifts of the corresponding monosubstituted compounds, devised by Fort and von R. Schleyer,[4] applies with accuracy in the present case. The chemical shifts of methyl adamantane-1-carboxylate and 1-(N,N-diethylamino)methyladamantane are given in the Experimental Section. The fair agreement between calculated and observed values for the protons of the ester **5a** allows for the safe assignment of its structure.

Pharmacology.—The hydrochlorides of the new substances (**4a–d**) were screened pharmacologically; this included studies of activity on CNS in mice,[5–7] analgetic activity in mice and rats,[8–11] antiinflammatory activity in rats and guinea pigs,[12,13] antipyretic activity in mice,[14] action on rabbits' cardiovascular system, action on the isolated rabbit heart,[15] antifibrillatory activity,[16] and action on the isolated guinea pig ileum.

None of the compounds showed in these tests anything worthy of note, unless an exception is made for a slight analgetic and antipyretic activity displayed by **4b**.

Experimental Section[17]

Adamantane-1-carboxamides (2).—The solution of the chloride from 0.015 mole of the acid **1**[18] in 20 ml of anhydrous Et_2O was added dropwise to a stirred solution of the appropriate amine (0.032 mole) in Et_2O (25 ml), cooled in an ice–water bath. A white precipitate was formed while stirring was continued for 0.5 hr. After evaporation of the solvent the residue was treated with 10% HCl and the colorless insoluble material was filtered, washed (H_2O), and recrystallized (MeOH–H_2O). Yields and physical constants of the amides thus obtained are given in Table I.

1-(N,N-Dialkylamino)methyladamantanes (3).—A solution of the amide **2** (0.012 mole) in 60 ml of anhydrous Et_2O was added dropwise to a stirred suspension of $LiAlH_4$ (0.013 mole) in Et_2O (30 ml) and the mixture was refluxed with vigorous stirring during 2–3 hr. After cooling, hydrolysis was accomplished with H_2O (0.5 ml), 0.5 ml of a 15% solution of NaOH, and H_2O (1.5 ml). The white precipitate formed was filtered and thoroughly washed (Et_2O). After drying and evaporation of the ether there was obtained a residue of the crude amine. All the amines thus obtained were oily and were characterized as their picrates (see Table II), except for the N-morpholinomethyl compound **3c** which had mp 60–64°. Since the analysis of this compound was satisfactory, the amines thus obtained were used, without further purification, for the Koch–Haaf carboxylation reaction.

3-(N,N-Dialkylamino)methyladamantane-1-carboxylic Acids (4).—The carboxylation reaction was conducted under the conditions used for the carboxylation of adamantane[3] and is described below in detail for the morpholino derivative **4c**.

A solution of HCO_2H (98–100%, 14 g, 0.24 mole) in *t*-BuOH (7.7 g, 0.08 mole) was added during 4–5 hr in a stirred solution of 6 g (0.02 mole) of the amine **3c** in 120 g of concentrated H_2SO_4 (94–96%, *d* 1.84) at 17–19°. The foaming grayish mixture was stirred for 15 hr at room temperature and was then poured in ice and extracted (Et_2O). Evaporation of the solvent gave 6.5 g of a mobile liquid of a characteristic odor (trimethylacetic acid). The acid aqueous phase was made alkaline with 40% NaOH and extracted (Et_2O), yielding 3.20 g (53%) of recovered amine, mp 59–63°. The alkaline phase was then neutralized to pH ~7 with AcOH, salted out with NaCl, and continuously extracted (Et_2O) during 20 hr. Evaporation of the solvent gave 1.70 g of a colorless solid, mp 175–180°. This was transformed into the hydrochloride salt, which was recrystallized from absolute EtOH–anhydrous Et_2O affording 0.8 g (11%) of a crystalline product (see Table III), corresponding to **4c**.

Methyl 3-(N,N-Diethylamino)methyladamantane-1-carboxylate (5a).—A suspension of **4a**·HCl (0.4 g) in Et_2O (20 ml) was treated with excess CH_2N_2 in Et_2O. The solid gradually passed into solution and the yellow solution obtained was left for some hours at room temperature. The solvent was evaporated and the residue was purified by chromatography on alumina. Elution with petroleum ether–Et_2O (1:1) gave a fraction (0.325 g) of a colorless oily product. Microdistillation of this material gave an analytically pure sample. *Anal.* ($C_{17}H_{29}NO_2$) C, H. Its nmr spectrum is examined below.

Methyl 3-(N-Piperidino)methyladamantane-1-carboxylate (5b).—The methyl ester of **4b**, obtained by this same procedure, was characterized by its **picrate,** mp 156–159°. *Anal.* ($C_{24}H_{32}N_4O_9$) C, H, N. The molecular weight of this salt determined spectrophotometrically[19] was found to be 513 (calcd 520.5).

1,3-[Bis(N-piperidino)methyl]adamantane (7). A. From the Amino Acid 4b.—The hydrochloride of **4b** (0.5 g) was refluxed with 5 ml of $SOCl_2$ for 30 min. After elimination of the excess reagent under vacuum and treatment with PhH to eliminate the last traces of $SOCl_2$, the corresponding **acid chloride** was obtained as a colorless solid (0.45 g), mp 207–210°. This was dissolved in 20 ml of anhydrous Et_2O, a solution of 1.5 g of piperidine in C_6H_6 was added, and the mixture refluxed for 2 hr. After evaporation of the solvent the solid residue was treated with alkali, saturated with NaCl, and extracted (Et_2O), yielding the **amine–amide 6** as a thick oil (0.55 g); **picrate,** mp 198–201° dec (absolute EtOH). *Anal.* ($C_{28}H_{39}N_5O_8$) C, H, N.

The amine–amide **6** (0.25 g) was reduced with 1.5 g of $LiAlH_4$ in a manner similar to the one already mentioned (*cf.* **2** → **3**). After decomposition of the complex and extraction (Et_2O), the ethereal phase was washed with 10% HCl. The aqueous acid phase was made alkaline, saturated with NaCl, and extracted

(4) R. C. Fort, Jr., and P. von R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).
(5) F. M. Berger, *J. Pharmacol. Exp. Ther.*, **93**, 470 (1948).
(6) J. R. Boissier, *Actualites Pharmacol.*, **12**, 7 (1959).
(7) C. Bianchi, *Arch. Int. Pharmacodyn. Ther.*, **111**, 227 (1957).
(8) E. Adami and E. Marazzi, *ibid.*, **107**, 322 (1956).
(9) C. Bianchi and J. Franceschini, *Brit. J. Pharmacol.*, **9**, 280 (1954).
(10) J. Reinhart and E. de Beer in "Biological Standardization," J. Burn, D. Finney, and L. Goodwin, Ed., 2nd ed, Oxford University Press, London, 1950, p 316.
(11) L. O. Randall and J. J. Selitto, *Arch. Int. Pharmacodyn. Ther.*, **111**, 409 (1957).
(12) C. V. Winder, J. Wax, V. Burr, M. Been, and C. E. Rosiere, *ibid.*, **116**, 261 (1958).
(13) C. A. Winter, International Symposium on Non-Steroidal Antiinflammatory Drugs, Sept 1964, Excerpta Medica Foundation, Amsterdam, p 190.
(14) C. Bianchi, B. Lumachi, and L. Pegrassi, *Arzneim.-Forsch.*, **17**, 246 (1967).
(15) I. Setnikar, *Farmaco, Ed. Sci.*, **11**, 750 (1956).
(16) G. Dawes, *Brit. J. Pharmacol.*, **1**, 90 (1946).
(17) Melting points were determined by the capillary tube method and are not corrected. Nmr spectra were measured at 60 Mc, using TMS as an internal standard in $CDCl_3$, at the Institut de Chimie des Substances Naturelles (Gif-sur-Yvette, France), through the courtesy of Professor E. Lederer.
(18) H. Stetter and E. Rauscher, *Chem. Ber.*, **93**, 1161 (1960).
(19) K. G. Cunningham, W. Dawson, and F. S. Spring, *J. Chem. Soc.*, 2305 (1951).

(Et_2O), yielding 0.17 g of the diamine **7**, as a colorless product, mp 37–41°; **picrate,** mp 226–228° dec (absolute EtOH). *Anal.* ($C_{31}H_{34}N_8O_{14}$) C, H.

B. From the Diamide 8.—Reduction of the dipiperidide **8**[20] (0.2 g) with $LiAlH_4$ by the same procedure as above gave 0.15 g of a colorless product, mp 38–41°; **picrate,** mp 225–227° dec.

Nmr Spectra. (a) Methyl Adamantane-1-carboxylate.—Peaks[21] at τ 8.10 (−0.12) (β-H), 8.00 (−0.12) (γ-H), 8.28 (+0.06) (δ-H), and 6.41 (CH_3); *cf.* the values in CCl_4 solution:[4] τ 8.12 (−0.10) (β-H), 8.01 (−0.11) (γ-H), 8.29 (+0.07) (δ-H), and 6.40 (CH_3).

(b) 1-(N,N-Diethylamino)methyladamantane (3a).—Peaks[21] at τ 8.51 (+0.29) (β-H), 8.06 (−0.06) (γ-H), 8.31 (+0.09) (δ-H), 9.05 (t) (NCH_2CH_3), 7.56 (q) (NCH_2CH_3), and 7.96 (s) ($CH_2N<$). It is interesting to note that the chemical shifts of the protons in positions β, γ, and δ are practically the same as those of 1-methyladamantane in CCl_4 solution:[4] τ 8.52 (+0.30) (β-H), 8.08 (−0.04) (γ-H), and 8.32 (+0.10) (δ-H).

(c) Methyl 3-(N,N-diethylamino)methyladamantane-1-carboxylate (5a).—The chemical shifts for the protons in positions a–e can be calculated[4] as shown in Table IV. Other peaks

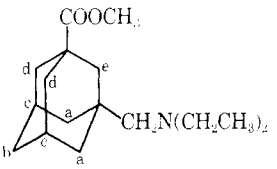

TABLE IV

Proton	Chemical shifts, τ — Calcd	Found
$4H_a$	8.22 + 0.06 + 0.29 = 8.57	8.55
$2H_b$	8.22 + 0.06 + 0.09 = 8.37	8.41
$2H_c$	8.12 − 0.12 − 0.06 = 7.94	7.96
$4H_d$	8.22 − 0.12 + 0.09 = 8.19	8.21
$2H_e$	8.22 − 0.12 + 0.29 = 8.39	8.41

are found at τ 9.05 (t) (NCH_2CH_3), 7.96 (s) ($CH_2N<$), 7.56 (q) (NCH_2CH_3), and 6.41 (s) ($COOCH_3$).

Acknowledgments.—The authors are indebted to the Microanalytical Laboratory of CIBA, Basel, for performing the microanalyses, to Professor E. Lederer, Gif-sur-Yvette, France, for the nmr spectra, and to the Director of De Angeli, Milan, for his cooperation.

(20) H. Stetter and C. Wulff, *Chem. Ber.*, **93**, 1366 (1960).

(21) The resonances of the protons are referred as in positions β, γ, and δ relative to the substituent. Values in parentheses are shifts from the values of adamantane in CCl_4 solution, *i.e.*, 8.22 for the CH_2 protons and 8.12 for the bridgehead protons (see ref 4).

Spirans. XVI. 9-Hydroxymethyl-3-azaspiro[5.5]undecanes[1,2]

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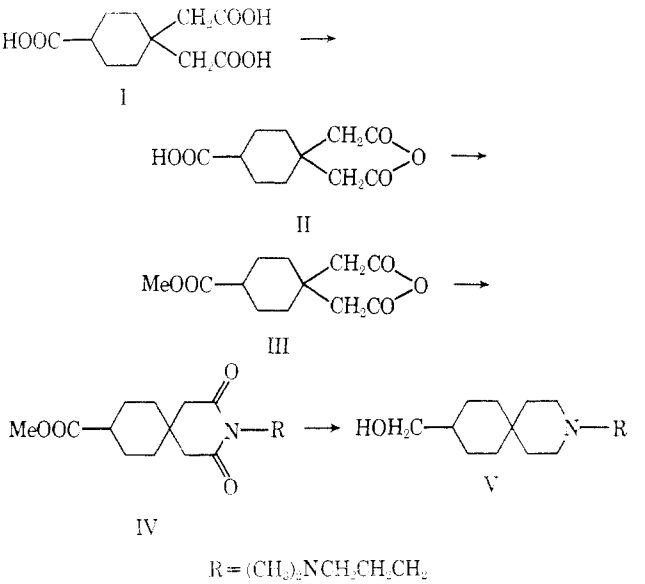
Received August 9, 1968

For some time we have been interested in placing a functional group into the 9 position of the 3-azaspiro-[5.5]undecane nucleus and studying its pharmacological properties. While substitution by such groups as alkyl, aryl, and trifluoromethyl which are relatively inert chemically have been made accessible from the starting ketones, substitution by more reactive functional groups have not been readily obtainable. We now wish to report a synthesis in which the hydroxymethyl group is present in the 9 position of the 3-azaspiro[5.5]-undecane nucleus. This group is amenable to various reactions which could produce other functional groupings.



R = $(CH_3)_2NCH_2CH_2CH_2$

The key intermediate in our synthesis was 4-carboxycyclohexane-1,1-diacetic acid[3] (I), which could be converted to the anhydride II by mild treatment with acetic anhydride or acetyl chloride. Although the reaction was selective with respect to the 1,1-diacetic acid substitution, some polymeric anhydride was always formed but the quantity could be limited by a short contact time. The polymeric anhydride could also be converted back to the starting acid I with very little loss in over-all yield. The conversion of the anhydride acid II to the anhydride methyl ester III by means of diazomethane was particularly rewarding with no attack on the anhydride moiety. Reaction of the ester anhydride III with 3-dimethylaminopropylamine gave IV without any amide formation from the methyl ester. Cyclization to the imide ester IV was completed at 180°. The product could be distilled easily and was reduced by $LiAlH_4$ to the hydroxymethyl base V.

The hydrochloride salt of V, when screened against mammary cancer cell cultures and KB tissue culture cells, had an activity at about 20 μg ml. The LD_{50} was 175 mg/kg. No remarkable reactions were noted in a general screen using rats for other pharmacological perimeters such as analgesia, sedation, and CNS stimulation, except for more foam cells than normal in the pathological examination of the autopsied animals.

Experimental Section[4]

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within 0.3% of the theoretical values. All compounds conformed to their ir spectra.

4-Carboxycyclohexane-1,1-diacetic Acid Anhydride (II). A.—A mixture of 25 g of acid I and 100 ml of AcCl was heated to

(1) Supported by the Geschickter Fund for Medical Research.

(2) Part XV: L. M. Rice, B. S. Sheth, K. R. Scott, and C. F. Geschickter, *J. Med. Chem.*, **12**, 126 (1969).

(3) L. M. Rice and K. R. Scott, *J. Org. Chem.*, **32**, 1966 (1967).

(4) Melting points were determined with a Thomas–Hoover apparatus and are corrected. Microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.