1-Phenylcycloalkylamine Derivatives. II.[1,2] Synthesis and Pharmacological Activity

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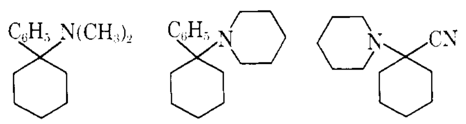
A series of N,N-substituted 1-arylcyclohexylamines was prepared mainly by the reaction of an arylmagnesium bromide and 1-dialkylaminocyclohexanecarbonitrile. As the cyclopentyl analog could not be obtained by this way, condensation of 1-phenylcyclopentylamine with pentamethylene dibromide in DMF was tried with success. These compounds were tested for their psychopharmacological properties. 1-[1-(2-Thienyl)cyclohexyl]piperidine (**16**) was found to be the most active.

The pharmacological properties of 1-(1-phenylcyclohexyl)piperidine (**7**)[3] (phenylcyclidine[4-6]), for which at the time of this investigation only one synthesis has been described,[6] stimulated the exploration of possible preparative routes applicable also to other members of the series.



5 7 27

Various attempts were made to prepare **7**. Piperidine did not substitute the halogen atom in phenylcyclohexyl chloride, but caused dehydrohalogenation; also the methylene group in 1-benzylpiperidine proved unreactive for condensation with pentamethylene bromide in the presence of NaH.

By another method, based on the early work of Bruylants,[7] a series of N-alkylated 1-phenylcyclohexylamines were obtained (Table I) from the corresponding alkylaminocyclohexanecarbonitriles (Table II). The mechanism of the Bruylants reaction has been the subject of many investigations,[6,8-11] which revealed that piperidinocyclohexanecarbonitrile (**27**) with PhMgBr gives **7**, whereas with PhLi the expected product, 1-piperidinocyclohexyl phenyl ketone is obtained.

The formation of **3** from N-ethylcyclohexanecarbonitrile (**25**) and 3 moles of PhLi suggests that the reaction proceeds through N-cyclohexylidenethylamine as an intermediate. This view is supported by the fact that Maddox, *et al.*,[12] obtained the above amine from N-cyclohexylidenethylamine and 2 moles of PhLi. The cyclopentyl analog of **7** could not be prepared this way,[8] but as described in the Experimental Section. An alternative route from 1-phenylcyclopentylamine and glutaric anhydride was unsuccessful.

Experimental Section

1-Piperidinocyclohexanecarbonitrile (27).—Piperidine (85 g, 1.0 mole) was carefully mixed with 84 ml of concentrated HCl and 200 g of ice–water, and the pH was adjusted to 3–4. To this solution, 98 g (1.0 mole) of cyclohexanone was added, followed by 68 g of KCN in 150 ml of H_2O without external cooling but with efficient stirring. After 2 hr the solution was allowed to stand overnight, and the crystalline precipitate was collected, washed (cold H_2O), and dried. The yield was 169–182 g (88–95%), mp 63–68°. This product was sufficiently pure for the next step. Recrystallization from EtOH raised the melting point to 68–70°.

Other alkylaminocycloalkanecarbonitriles, prepared accordingly, are listed in Table II.

N,N-Dimethyl-1-phenylcyclohexylamine (5).—A mixture of 8.7 g of 1-phenylcyclohexylamine, 7.8 g of 88% HCO_2H, and 12.5 g of 35% CH_2O was refluxed for 5 hr, cooled, and made alkaline. The base was extracted (Et_2O), the solution was dried and concentrated, and the product distilled.

N-Methyl-1-phenylcyclohexylamine (1) (Procedure A).—A solution of 27 g of N-(phenylcyclohexyl)formamide[1] in C_6H_6 was slowly added to 16.0 g of LAH in 500 ml of Et_2O. After 1 hr of reflux the mixture was decomposed and the basic material separated and distilled.

N-Ethyl-1-phenylcyclohexylamine (3) (Procedure B).—A solution of 76 g (0.5 mole) of **25** in 200 ml of Et_2O was added to PhLi [prepared from 236 g (1.5 moles) of PhBr and 25 g of Li ribbon in 800 ml of Et_2O] at such a rate that a gentle reflux was maintained. The mixture was heated and stirred 30 min, then filtered quickly, and the filtrate cautiously was poured on crushed ice. The organic layer was separated, dried, and fractionally distilled.

1-(1-Phenylcyclohexyl)piperidine (7) (Procedure C).—A solution of 76.8 g of **27** in Et_2O-C_6H_6 was added slowly to PhMgBr prepared from 110 g of PhBr and 17.3 g of Mg in 400 ml of Et_2O. A viscous precipitate formed and stirring became difficult. After the addition was completed the mixture was allowed to stand for 3 hr, then poured into ice-NH_4Cl. The Et_2O layer was separated and washed (H_2O). The base was extracted with dilute HCl, liberated again with concentrated NH_4OH, extracted with Et_2O, dried, and distilled. The distillate which solidified was recrystallized from EtOH.

1-Dimethylaminocyclopentyl Phenyl Ketone (19).[13]—To a solution of PhLi (from 118 g of PhBr and 10 g of Li in 400 ml of Et_2O) was added 34.5 g (0.25 mole) of **31** in 100 ml of Et_2O and heated 1 hr. The resultant solution was filtered through glass wool and cautiously treated with cold, diluted HCl. The amine was liberated and distilled.

α-(1-Dimethylaminocyclopentyl)benzyl Alcohol (22).—The foregoing ketone (15 g) in 100 ml of Et_2O was added to 4 g of LAH in 300 ml of Et_2O and refluxed 1 hr. The mixture was decomposed, and the basic product was isolated.

1-(1-Phenylcyclopentyl)piperidine (18).—A mixture of 8.0 g of 1-phenylcyclopentylamine,[1] 11.5 g of 1,5-dibromopentane,

(1) Part I: A. Kalir and Z. Pelah, *Israel J. Chem.*, **5**, 223 (1967).
(2) Presented in part at the 34th Meeting of the Israel Chemical Society, Jerusalem, Dec 1964; *Israel J. Chem.*, **2**, 312 (1964), and at the Meeting of the Israel Physiological and Pharmacological Society, Rehovoth, April 1966.
(3) Numbers refer to Tables I and II.
(4) A. J. Catenacci, *Fed. Proc.*, **17**, 357 (1958).
(5) E. F. Domino, *Int. Rev. Neurobiol.*, **6**, 303 (1963).
(6) Z. Welvart, *C. R. Acad. Sci., Paris*, **250**, 1870 (1960).
(7) P. Bruylants, *Bull. Soc. Chim. Belges*, **33**, 467 (1924).
(8) J. Sansoulet, C. Tackx, and Z. Welvart, *C. R. Acad. Sci., Paris*, **250**, 4370 (1960).
(9) G. Chauviere, B. Tchoubar, and Z. Welvart, *Bull. Soc. Chim. Fr.*, 1428 (1963).
(10) (a) J. Yoshimura, Y. Ohgo, and T. Sato, *J. Am. Chem. Soc.*, **86**, 3858 (1964); (b) *Bull. Chem. Soc. Japan*, **38**, 1809 (1965).
(11) B. Hermans, P. van Daele, C. van de Westeringh, C. van der Eycken, J. Boey, and P. A. J. Janssen, *J. Med. Chem.*, **8**, 851 (1965).
(12) H. Maddox, E. F. Godefroi, and R. F. Parcell, *ibid.*, **8**, 230 (1965).
(13) The pharmacological properties of 1-phenylcyclopentylamine derivatives have been reported by L. Buchel, Y. Levy, and O. Tanguy, *Therapie*, **20**, 467 (1965), but with no preparative details and physicochemical data.

TABLE I

1-ARYLCYCLOALKYLAMINES

No.[a]	Ar	R′	R″	Method	Yield, %	Bp (mm) or mp, °C	Formula	Analyses
				A. Cyclohexylamine Derivatives				
1	Ph[b]	H	CH_3	A	85	99.5 (1)	$C_{13}H_{19}N$	C, H, N
1a						187–189	$C_{13}H_{20}ClN$	C, H, Cl, N
1b						169–171	$C_{19}H_{22}N_4O_7$	C, H, N
2	4-ClC_6H_4	H	CH_3	A	60	121–122 (1)	$C_{13}H_{18}ClN$	N
2b						194–195	$C_{19}H_{21}ClN_4O_7$	C, H, Cl, N
3	Ph[b]	H	C_2H_5	A	55	103–105 (0.5)	$C_{14}H_{21}N$[c]	C, H, N
				B	69			
3a						236–238	$C_{14}H_{22}ClN$	C, H, Cl, N
3b						164–166	$C_{20}H_{24}N_4O_7$	C, H, N
4	Ph[b]	H	$CH(CH_3)_2$	B	41	107–108 (0.6)	$C_{15}H_{23}N$	C, H
5	Ph[b]	CH_3	CH_3	See text	91	111–112 (0.5)	$C_{14}H_{21}N$	C, H
						44–46		
5b						183–184	$C_{20}H_{24}N_4O_7$	C, H
5c					87	238–240 dec	$C_{15}H_{24}IN$	C, H
6	Ph[b]	$-(CH_2)_4-$		C	45	124–125 (0.7)	$C_{16}H_{23}N$	C, H
						44–46		
6a						229–230	$C_{16}H_{24}ClN$	C, H
7	Ph[b]	$-(CH_2)_5-$		C	73	140–145 (1.5)	$C_{17}H_{25}N$	C, H, N
						44–45		
7a						233–234	$C_{17}H_{26}ClN$	Cl, N
7b						179–180	$C_{23}H_{28}N_4O_7$	C, H
7c					83	119–120	$C_{18}H_{28}IN$	C, H, N
8	4-FC_6H_4	$-(CH_2)_5-$		C	55	130–132 (0.8)	$C_{17}H_{24}FN$	C, H, F
8a						225–226	$C_{17}H_{25}ClFN$	C, H, F
8b						197–198	$C_{23}H_{27}FN_4O_7$	C, H, F, N
9	4-ClC_6H_4	$-(CH_2)_5-$		C	48	165–167 (0.8)	$C_{17}H_{24}ClN$	C, H
						37		
9a						220–221	$C_{17}H_{25}Cl_2N$	C, H
9b						199–200	$C_{23}H_{27}ClN_4O_7$	C, H
10	4-$F_3CC_6H_4$	$-(CH_2)_5-$		C	20	135–140 (0.6)	$C_{18}H_{24}F_3N$	C, H, F
10a						216–217	$C_{18}H_{25}ClF_3N$	F, N
10b						210–211	$C_{24}H_{27}F_3N_4O_7$	F
11	4-$CH_3OC_6H_4$[b]	$-(CH_2)_5-$		C	43	180–185 (1.5)	$C_{18}H_{27}NO$	N
						48–50		
11a						245	$C_{18}H_{28}ClNO$	C, H
11b						137–138	$C_{24}H_{30}N_4O_8$	C, H
12	4-$CH_3C_6H_4$[b]	$-(CH_2)_5-$		C	48	66–67	$C_{18}H_{27}N$	C, H, N
13	$PhCH_2$	$-(CH_2)_5-$		C	47	71.5–72.5	$C_{18}H_{27}N$	C, H, N
13a						238–239	$C_{18}H_{28}ClN$	C, H, Cl, N
14	Ph	$(-CH_2CH_2)_2C(CH_3)_2$		C	77	80–82	$C_{19}H_{29}N$	C, H, N
15	Ph	$(-CH_2CH_2)_2N(CH_3)$		C	33	160–165 (2)	$C_{17}H_{26}N_2$	C, H, N
						69–70		
15b						258–260	$C_{29}H_{32}N_8O_{14}$	C, H, N
16	2-Thienyl	$-(CH_2)_5-$		C	59	144 (1.2)	$C_{15}H_{23}NS$	C, H
						37–38		
16a						230–235	$C_{15}H_{24}ClNS$	C, H, Cl, N
17	2-Thienyl	$-(CH_2)_4-$		C	44	120 (0.2)	$C_{14}H_{21}NS$	C, H, N
						44.5–45		
17a						187–189	$C_{14}H_{22}ClNS$	N
17b						145–147	$C_{14}H_{24}N_4O_7S$	C, H
				B. Cyclopentylamine Derivatives				
18	Ph	$-(CH_2)_5-$			70	49.5–50.5	$C_{16}H_{23}N$	C, H, N
18b						171–173	$C_{22}H_{26}N_4O_7$	C, H
19	PhCO	CH_3	CH_3		75	175 (25)	$C_{14}H_{19}NO$	C, H,N
						63–65		
20	PhCO	$-(CH_2)_4-$			58	188–190 (25)	$C_{16}H_{21}NO$[d]	C, H, N
20a						155–157	$C_{16}H_{22}ClNO$	C, H, N
21	PhCO	$-(CH_2)_5-$			76	198–200 (25)	$C_{17}H_{23}NO$[e]	C, H
21a						183–185	$C_{17}H_{24}ClNO$	C, H, Cl
21b						165–166	$C_{23}H_{26}N_4O_8$	C, H
22	PhCHOH	CH_3	CH_3		95	82–84	$C_{14}H_{21}NO$	C, H, N
23	PhCHOH	$-(CH_2)_4-$			98	203–205 (20)	$C_{16}H_{23}NO$[f]	C, H, N
24	PhCHOH	$-(CH_2)_5-$			98	68–69	$C_{17}H_{25}NO$	C, H, N

[a] a = hydrochloride, b = picrate, c = methiodide. [b] Reference 12. [c] n^{20}_{D} 1.5324. [d] n^{28}_{D} 1.5481. [e] n^{28}_{D} 1.5465. [f] n^{17}_{D} 1.5517.

TABLE II

1-ALKYLAMINOCYCLOALKANECARBONITRILES

No.	n	R′	R″	Yield, %	Bp (mm) or mp, °C	Formula	Analyses	n_D (t, °C)
25	5	H	C_2H_5	92	116 (26)	$C_9H_{16}N_2$	N	1.4653 (25)
26	5	$-(CH_2)_4-$		72	94–96 (0.9) 24–26	$C_{11}H_{18}N_2$	C, H	
27[a]	5	$-(CH_2)_5-$			151–152	$C_{18}H_{23}N_5O_7$	C, H	
28	5	$(-CH_2CH_2)_2C(CH_3)_2$		63	58–59	$C_{14}H_{24}N_2$	C, H	
29	5	$CH_2CH_2N(CH_3)CH_2CH_2$		49[b]	143–145 (25)	$C_{12}H_{21}N_3$	C, H, N	
30	4	H	C_2H_5	53	99 (26)	$C_8H_{14}N_2$	C, H	1.4560 (26)
31	4	CH_3	CH_3	89	99 (25)	$C_8H_{14}N_2$	N	1.4541 (27)
32	4	$-(CH_2)_5-$		79	125 (24)	$C_{10}H_{16}N_2$	C, H	1.4802 (26)
33	4	$-(CH_2)_5-$		85	145 (30)	$C_{11}H_{18}N_2$	C, H, N	1.4882 (27)

[a] Picrate. [b] A small amount of a by-product, mp 200–201° dec, was identified as N,N′-bis(1-cyanocyclohexyl)piperazine. *Anal.* ($C_{18}H_{28}N_4$) C, H.

TABLE III

EFFECTS OF PHENCYCLIDINE AND ITS ANALOGS ON FORCED MOTOR ACTIVITY (MICE), CONDITIONED AVOIDANCE RESPONSE (RATS), AND DIGGING ACTIVITY (GERBILS)

	Forced motor act. (rotarod)			CAR		Gerbil digging		
		% redn in performance after					No. of animals out of 4 which did not pass the sand barrier after	
No.	Dose, mg/kg	30 min	60 min	Dose, mg/kg	% reduction in response	Dose, mg/kg	30 min	60 min
1a	5	48	0	5	6	5	3	1
2	10	0	0	10	0	10	0	0
3a	1	8	0	1	44	1	2	2
	2	91	43			2	4	3
5	6	21	0	8	10	5	1	0
	7	47	17			7	4	2
6a	2	0	0	3	0			
	3	30	0	4	7	2	0	1
	4	76	46	6	60	3	4	4
				8	100			
7a	4	65	40	3	25	1	1	1
						2	3	4
7c	15	0	0	10	0	10	0	0
8a	10	10	0	10	0	5	2	1
						7	4	2
9a	10	0	0	10	0	10	1	0
10a	10	0	0	10	0	10	0	0
11a	10	0	0	10	0	5	0	0
						10	2	2
13a	30	0	0	10	0	10	0	0
14	20	0	0	10	0	10	1	2
16a	2	10	0	1	25	1	2	2
	3	58	34	2	100	2	4	3
	4	98	68					
18	5	0	0	5	6	5	2	2
	8	15	0	8	71			
	15	43	0					
19	10	0	0	10	0	10	0	0
20a	10	0	0	10	0	10	0	0
21	10	0	0	10	0	10	0	0

8.0 g of anhydrous K_2CO_3, and 50 ml of dry DMF was stirred and heated. At 50–55° an exothermic reaction occurred and the temperature rose to 95–100°. The content was heated 1 hr on a water bath and poured into cold H_2O, and the product was extracted with Et_2O, distilled, and recrystallized.

N-(1-Phenylcyclopentyl)glutaramic Acid.—1-Phenylcyclopentylamine (5.1 g) was mixed with 3.52 g of glutaric anhydride. The reaction was exothermic and after short heating at 180–200° the product was cooled and recrystallized (EtOH); yield 7.8 g (89%), mp 172–173°. *Anal.* ($C_{16}H_{21}NO_3$) C, H. The product did not cyclize when heated to 230–250° but decomposed to 1-phenylcyclopentene.

Pharmacological Tests. Methods.—Saline solutions of the compounds were adjusted so that a volume of 0.1 ml/10 g was administered subcutaneously to mice and gerbils, and 0.2 ml/100 g to rats. Monkeys were injected (0.25 ml/kg) into the saphena vein. In cats the maximal volume injected was 0.2 ml. In all cases the animals used were of either sex. Hydrochlorides of **2**, **5**, and **14** were prepared by dissolving the materials in dilute HCl and the solutions were then neutralized with phosphate buffer before injection.

Conditional Avoidance Response.—Inbred albino rats, weighing 200–300 g, were trained to jump in a shuttle box[14] to avoid a 65-V electric shock. The condition was a photic stimulus of 5-sec duration presented every 30 sec. An animal was considered fully trained when at least 80% of the possible correct responses were made in a period of 25 min. Four fully trained animals were administered each dose level and tested 1 hr after injection.

Forced Motor Activity (Rotating Rod).—Random-bred albino mice, 20–25 g, were trained to remain on a rotating rod which turned five times per minute.[15] Six trained animals were injected with each dose level of the compounds and tested 30 and 60 min

(14) D. Bovet, C. L. Gatti, and M. Frank, *Sci. Rept. Ist. Super. Sanita*, **1**, 127 (1961).

(15) N. W. Dunham and T. S. Miya, *J. Amer. Pharm. Ass.*, **46**, 208 (1957).

TABLE IV

EFFECTS OF PHENCYCLIDINE AND ITS ANALOGS ON THE BEHAVIOR OF MONKEYS AND CATS AND ON THE EXPLORATORY ACTIVITY OF RATS

	Main behavioral changes				Hall's open field[a]					
						% of normal				
No.	Dose, μg/kg	Monkeys	Dose, μg (intraventric)	Cats	Dose, mg/kg	Ambulation	Rearing	Entrance center	No. of fecal boluses	Preening
1a	50	None								
	100	None			5	112	15	NC	DEC	DEC*
3a	50	None	20	Sl ataxia	1	90	31	DEC	NC	DEC*
	100	None	30	Ataxia, tameness						
	250	Ataxia, sedation, sl tameness								
5	100	None			6	100	35	DEC	NC	DEC
					8	90	20	DEC	DEC	DEC*
6a	50	None								
	100	Sl sedation, sl tameness			1	161	79	DEC	DEC	DEC
	250	Ataxia, sl tameness								
	500	Strong ataxia, tameness								
7a	50	None	20	None	3	86	48	DEC	NC	DEC
	100	Sl ataxia, sl tameness	50	Sedation, twitching of eyelids, Appearance of nictitating membrane, piloerection						
	250	Strong ataxia	200	Sedation, stupor, twitching of eyelids, Appearance of nictitating membrane, piloerection						
7c	500	None								
10a			200	None						
11a			200	None						
14			200	None						
16a	50	Sedation, tameness, sl ataxia	20	Sedation, tameness, no ataxia	1	150	54	INC	DEC	DEC*
	100	Strong ataxia, tameness	30	Ataxia, sl sedation						
	250	Strong ataxia, "absences"								
18	100	Calmness								
	250	Tameness								

[a] DEC = decrease, INC = increase, NC = no change, * = ataxia was also observed.

after administration. A stay of 2 min on the rod was taken as 100% performance.

Hall's Open Field. The exploratory behavior of albino adult rats was studied in a field of 1.15 × 1.15 m divided into 36 equal squares, for 2 min. The following parameters were recorded: ambulation, rearing, times approaching the center of the field, preening, and the number of boluses excreted (emotional defecation). Results were scored as described by Brimblecombe.[16] Four animals were administered each dose level and tested 1 hr thereafter. Control rats received saline.

Digging Test.—The gerbil (*Meriones tristrami*) shows an aptitude to dig when placed on sand. Random-bred gerbils of an albino strain,[17] weighing 50–80 g, were tested in a cage with two compartments separated by a trough filled with sand.[18] The animal was placed in one compartment 5 min before the test while the sand was covered. Then the cover was removed and digging activity was observed through a mirror placed above the cage. This activity was checked four times prior to and on the day of the experiment. The gerbils were tested 30 and 60 min after administration of the compounds and if they did not cross within 5 min after removal of the cover, the response was recorded as a "failure." Saline-injected animals crossed the sand barrier within 1–2 min.

Behavior of Monkeys.—Adults rhesus monkeys were kept in spacious cages and their behavior was followed up several hours after administration of the compounds. A behavior sheet similar to that described by Norton[19] was used for assessment. In most cases four animals were administered each dose level.

Intracerebroventricular Injections.—In cats a Collison canula was implanted into the left lateral ventricle under pentobarbital anesthesia and aseptic conditions. The animals were used 1 week after operation.

Results and Discussion

The main results are presented in Tables III and IV. For comparison those obtained with **7a** (phencyclidine) and **3a** (cyclohexamine) are included. The most active of the newly synthetized compounds were **16a** and **6a**.

(16) R. H. Brimblecombe, *Psychopharmacologia*, **4**, 139 (1963).

(17) J. Naftali and J. Wolf, *Bull. Res. Council Israel*, **5B**, 189 (1955).

(18) Anonymous, *Triangle, Sandoz J. Med. Sci.*, **4**, 244 (1960).

(19) S. Norton in "Psychotropic Drugs," S. Garattini and V. Ghetti, Ed., Elsevier Publishing Co., Amsterdam, 1957, p 73.

Rats administered with 2 mg/kg of **16a** or 8 mg/kg of **6a** showed a total disruption of learned behavior. The animals jumped haphazardly from one side of the shuttle box to the other, disregarding both the conditioned and the unconditioned stimulus. A parallelism existed between the activity of all compounds on the rotating rod test and on the conditioned avoidance response, *i.e.*, substances were either active or inactive in both tests.

Compounds **16a** and **6a** were the only compounds which produced, in spite of a pronounced ataxia, also a considerable increase in ambulation of rats. Most of the compounds consistently decreased the emotional defecation. This could be interpreted as a diminished fear, though the reduction in center entrances would be against this view. The only notable exception was **16a**.

The digging activity of the gerbils appeared to be a sensitive method for testing phenylcyclohexylamine derivatives, since this behavior was affected even by compounds which were inactive in the rotating rod and conditioned avoidance response tests.

Neither 30 μg/kg of **16a**, 50 μg/kg of **6a**, nor 50–100 μg/kg of **3a** caused noticeable behavioral changes in monkeys. Higher doses of these compounds produced sedation and tameness. For instance, it was possible to introduce a finger of the experimenter into the mouth of monkeys without an attempt by these to bite. This was impossible in the preinjection state. There were occasional licking movements and twitching of eyelids. The animals looked around indifferently and reacted slowly to painful stimulus. Still higher doses caused also ataxia. The animals recovered their habitual behavior after 1.5–4 hr of injection. Again in this test compound **16a** was the most active one.

Considering the chemical changes in the structure of the phenylcyclohexylamine molecule and the respective pharmacological activity, it appears that halogen substitution in the phenyl ring decreases the psychotropic activity. In contrast, thienyl instead of phenyl promotes activity. Thus **16a** was considerably more active than **7a** when compared on a weight basis.

Also, variation of the aminoalkyl group alters the pharmacological activity of the molecule. For example, N-methylamino- (**1**), N,N-dimethylamino- (**5**), and 4,4-dimethylpiperidino- (**14**) analogs were considerably less active than the N-ethylamino derivative (**3**) or **7** itself. Quaternization (**7c**) renders **7** totally inactive, even when administered intracerebroventricularly in order to by-pass the blood-brain barrier.

Spasmolytics. I. 3-Tropanyl 2-Arylacrylates and 3-Tropanyl 2-Arylhydracrylates[1]

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Synthesis and biological activities of a series of 3-tropanyl 2-arylacrylates and a series of 3-tropanyl 2-arylhydracrylates are described. The acrylates had spasmolytic activity without anticholinergic effect. In contrast the hydracrylates did not show this separation.

Since the advent of synthetic anticholinergic spasmolytic drugs, there has been an intensive effort to discover agents with lessened anticholinergic (dryness of the mouth, blurring of vision, urinary hesitancy) side effects. Though a papaverine-like or musculotropic kind of spasmolytic action has been sought, papaverine and its analogs have not been very useful clinically because of their poor oral efficacy and cardiovascular side effects. In 1958, Bachrach,[2] summarizing the literature on anticholinergic drugs, concluded that none of the synthetic agents exhibited specificity for any particular organ function or segment of the gastrointestinal tract. Further, he noted that there was no single anticholinergic of choice for any gastrointestinal disturbance unless it is atropine or belladonna because of low cost. Five years later, Friend concluded that atropine and belladonna were in "no immediate danger of being replaced" by new synthetic agents;[3] the situation is little changed today.

A major objective of synthetic work in this area has been to separate the side effects from the desired antisecretory and antispasmodic effects. Many different structural variations in both the tropic acid and tropine moieties have been made with atropine, but none have completely eliminated the side effects.

For this study we wanted to determine if this separation could be achieved by substitution in the benzene ring of atropine. The intermediate tropic acids (Table I) were prepared from the appropriately substituted phenylacetic acids by the method of Blicke, *et al.*,[4] in varying yields. For the esterification step available literature suggested that the known sequences leading to atropine gave only moderate yields. For example, *p*-fluoroatropine, the only reported nuclear-substituted atropine, was made in 26% yield by Berger, *et al.*,[5] using a modified Wolffenstein and Mamlock[6] procedure. One possible reason for this low yield was thought to be the absence of a solvent in the esterification step.

In our work when dry pyridine was added the product was the corresponding acrylate I; in contrast, when dry DMF was used and then acid hydrolysis of the protective O-acetyl group, it gave the expected hydracrylate II (see Chart I). This facile dehydration–deacetylation reaction in the related acylscopolamines has been studied in detail by Garrett,[7] who found that it occurred during basic, but not acid, hydrolysis.

The pure hydracrylates (Table II) were obtained in modest yields. It is of interest that Schmidt, *et al.*,[8] have modified this procedure using microquantities of tropine hydrochloride and O-acetyltropic acid chloride, to give pure atropine in reproducible yields of 70%.

Experimental Section

Where analyses are indicated by elements only, the analytical results obtained for those elements were within ±0.4% of the calculated values.

Chemistry.—Melting points were determined in open capillary tubes using the Thomas–Hoover Uni-Melt and are uncorrected.

Substituted Phenylacetic Acids.—2-Chloro-, 3-chloro-, and 4-methylphenylacetic acids were available commercially. 4-Chloro- and 4-bromophenylacetic acids were prepared from the nitriles by acid hydrolysis.[9] 2,6-Dichlorophenylacetic acid was prepared from the nitrile in 52% yield by saponification with KOH in ethylene glycol. 4-*t*-Butylphenylacetic acid was prepared by carbonating the Grignard reagent of 4-*t*-butylbenzyl chloride[10] which was prepared from *t*-butylbenzene.

Tropic acids (Table I) were prepared by adding CH_2O to the Ivanov reagent prepared from the appropriately substituted phenylacetic acid and *i*-PrMgCl according to Blicke, *et al.*[4]

2-(4-Trifluoromethylphenyl)-2-hydroxypropionic acid was prepared by the general method used by Skerrett and Woodcock.[11] A Grignard reagent was prepared by adding 246.5 g (1.09 moles) of 4-bromobenzotrifluoride to 26.6 g (1.09 g-atoms) of Mg in Et_2O and 10 drops of 3 *M* EtMgBr in 2 hr with stirring. The solution was heated at reflux temperature for 1.5 hr and cooled with ice water. Pyruvic acid (32 g, 0.365 mole) in Et_2O (100 ml) was added in 45 min, and the mixture was heated at reflux temperature for 20 hr, cooled to 5°, and decomposed with 10% H_2SO_4. After filtration through Filtercel, the organic layer was collected and extracted with 10% NaOH. Acidification with HCl and extraction (Et_2O), gave after drying and evaporation of the Et_2O, a residue which, on recrystallization from C_6H_6–hexane,

(1) Presented before the Division of Medicinal Chemistry at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968.

(2) W. H. Bachrach, *Am. J. Digest. Diseases*, **3**, 743 (1958).

(3) D. G. Friend, *Clin. Pharmacol. Therap.*, **4**, 559 (1963).

(4) F. F. Blicke, H. Raffelson, and B. Barna, *J. Am. Chem. Soc.*, **74**, 253 (1952).

(5) R. S. Berger, A. E. Jacobson, and A. A. Kondritzer, *J. Org. Chem.*, **22**, 451 (1957).

(6) R. Wolffenstein and L. Mamlock, *Chem. Ber.*, **41**, 723 (1908).

(7) E. R. Garrett, *J. Am. Chem. Soc.*, **79**, 1071 (1957).

(8) G. C. Schmidt, T. E. Eling, and J. C. Drach, *J. Pharm. Sci.*, **56**, 251 (1967).

(9) H. Gilman and A. H. Blatt, "Organic Syntheses," Coll. Vol. I, 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1944, p 436.

(10) E. E. Royals and R. N. Prasad, *J. Am. Chem. Soc.*, **77**, 1696 (1955).

(11) E. J. Skerrett and D. Woodcock, *J. Chem. Soc.*, 2805 (1952).