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).

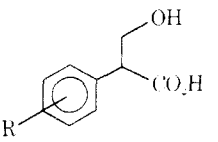
(8) G. C. Schmidt, T. E. Eling, and J. C. Drach, *J. Pharm. Sci.*, **56**, 251 (1967).

(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).

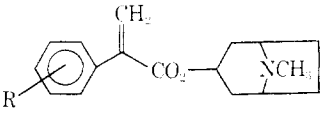
TABLE I
TROPIC ACIDS



Compd	R	Mp, °C	Recrystn solvent[a]	Yield,[b] %	Formula	Analyses
1	4-Cl	142–143	A	59	$C_9H_9ClO_3$	C, H, Cl
2	3-Cl	Oil		58.1[c,d]	$C_9H_9ClO_3$	
3	2-Cl	89–91	B	47	$C_9H_9ClO_3$	C, H, Cl
4	2,6-Cl_2	Oil		89.5[c,d]	$C_9H_8Cl_2O_3$	
5	4-Br	144.5–145	A	63.3	$C_9H_9BrO_3$	C, H, Br
6	4-CH_3O	127–128.5	A	54.3	$C_{10}H_{12}O_4$	C, H
7	4-*t*-Bu	120–121.5	C	41.7[c]	$C_{13}H_{18}O_3$	C, H
8	4-CH_3	118.5–119.5	A	18.6	$C_{10}H_{12}O_3$	C, H

[a] A = H_2O, B = PhMe, C = Et_2O-petroleum ether, D = *i*-PrOH, E = *i*-PrOH–EtOH, F = MeCN, G = petroleum ether, H = dioxane, I = MeOH–Et_2O, J = Et_2O, K = Me_2CO–Et_2O, L = hexane. [b] Yields are for pure products except where noted. [c] Yield of crude product. [d] Compound was used without purification.

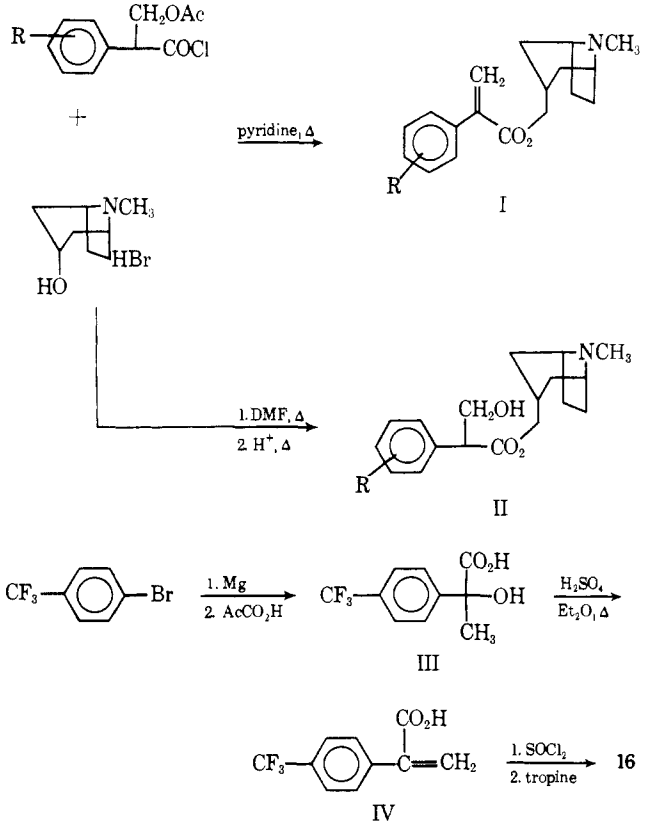
TABLE II
3-TROPANYL 2-ARYLACRYLATE HYDROCHLORIDES



Compd	R	Mp, °C	Recrystn solvent[a]	Yield,[b] %	Formula	Analyses
9	4-Cl	257–258 dec	A	20.1	$C_{17}H_{20}ClNO_2 \cdot HCl$	C, H, N, Cl
10	3-Cl	229.5–230.5 dec	D	19.3	$C_{17}H_{20}ClNO_2 \cdot HCl$	C, H, N, Cl
11	2-Cl	251.5–252.5 dec	E	11.0	$C_{17}H_{20}ClNO_2 \cdot HCl$	C, H, N, Cl
12	2,6-Cl_2	241–242	F	20.5	$C_{17}H_{19}Cl_2NO_2 \cdot HCl$	C, H, N, Cl
13	4-Br	255.5–256.5 dec	A	57.2	$C_{17}H_{20}BrNO_2 \cdot HCl$	C, H, N, Cl
14	4-CH_3O	77.5–78.0	G	10.3	$C_{18}H_{23}NO_3$	C, H, N
15	4-*t*-Bu	233–234.5	H	16.8	$C_{21}H_{30}NO_2 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl
16	4-CF_3[c]	59–61	L	21.2	$C_{18}H_{20}F_3NO_2 \cdot 0.25H_2O$	C, H, N

[a] See footnote *a* of Table I. [b] Yields are of pure product. [c] Yield of crude product.

CHART I



gave 40 g (47%) of pure product, mp 119–119.5°. *Anal.* ($C_{10}H_9F_3O_3$) C, H.

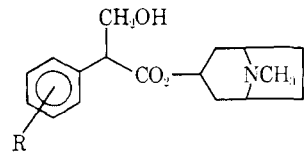
2-(4-Trifluoromethylphenyl)acrylic Acid.—2-(4-Trifluoromethylphenyl)-2-hydroxypropionic acid (17 g) in Et_2O (100 ml) was added with stirring to 75 ml of concentrated H_2SO_4. The mixture was heated on the steam bath for 1 hr, cooled, and poured onto ice. The product was extracted (Et_2O) and the resulting solution was washed (H_2O) and dried. Evaporation of the ether gave a quantitative yield of oil devoid of OH absorption which was used without further purification.

3-Tropanyl 2-(4-Trifluoromethylphenyl)acrylate Quarterhydrate (16).—The oily 2-(4-trifluoromethylphenyl)acrylic acid (about 15 g) was dissolved in 35 ml of dry C_6H_6, and 35 ml of $SOCl_2$ was added. The mixture was heated at reflux for 2 hr, C_6H_6 and excess $SOCl_2$ were removed, and three separate portions of dry C_6H_6 were added and removed in the same way. The residue (17 g, 0.073 mole) was dissolved in 50 ml of dry C_6H_6, and dry tropine (20.5 g, 0.145 mole) in 50 ml of dry C_6H_6 was added in 0.5 hr with stirring. The mixture was stirred at ambient temperature for 3 hr and filtered. The filtrate was washed (H_2O) until neutral and extracted three times with 10% HCl. This solution was made basic with 40% NaOH and the product was extracted into Et_2O which was washed, dried, and evaporated to give 5.3 g of an oil which crystallized from hexane, mp 59–61°. See Table II for additional details.

3-Tropanyl 2-Arylacrylates (Table II).[12]—The following procedure for the preparation of 3-tropanyl-2-(*p*-chlorophenyl)acrylic acid (**9**) illustrates the method used to prepare compounds **9–15**. A mixture of 20.1 g (0.10 mole) of *p*-chlorotropic acid and AcCl (50 ml) was warmed gently until a clear solution was obtained, and the solution was heated at reflux for 1 hr. After removal of the excess AcCl *in vacuo*, 100 ml of $SOCl_2$ was added, and the mixture was heated at reflux for 1 hr. Excess $SOCl_2$ was removed under reduced pressure with C_6H_6 as above. Tropine hydro-

(12) H. C. Caldwell and W. G. Groves, U. S. Patent 3,308,129 (1967).

TABLE III
3-TROPANYL 2-ARYLHYDRACRYLATES



Compd	R	Mp, °C	Recrystn solvent[a]	Yield,[b] %	Formula[d]
17	4-Cl	189–190	I	12.4	$C_{17}H_{22}ClNO_3 \cdot C_6H_{13}NO_3S$[c]
18	4-Br	97–98.5	J	24.8	$C_{17}H_{22}BrNO_3$
19	4-CH_3O	92.5–93.5	J	29	$C_{18}H_{25}NO_4$
20	4-CH_3	110–111	K	13.3	$C_{18}H_{25}NO_3$[e]

[a] See footnote *a* of Table I. [b] Yields are of pure product. [c] Hexamate. [d] All compounds were analyzed for C, H, N. [e] C: calcd, 71.26; found, 71.77, 72.00.

bromide[3] (20 g, 0.09 mole) and dry pyridine (35 ml) were added, and the mixture was heated on the steam bath for 1 hr. After cooling, H_2O was added and the product was collected and recrystallized (H_2O) to give the crude HBr salt. It was converted to the HCl salt *via* the free base.

3-Tropanyl 2-Arylhydracrylates (Table III).—The general esterification procedure as described above was used, but 20 ml of dry DMF, instead of dry pyridine, was added to a 0.1 mole run.

Pharmacological Methods.—The drugs were administered orally by stomach tube in all cases.

Minimum Lethal Dose and Observation of Overt Effects.—Groups of three mice were administered various doses of test drug. Observations for behavioral changes, impairment of reflexes, mydriasis, and lethality were made. The lowest dose causing death was defined as the MLD. Measurements of pupil diameter served to indicate possible anticholinergic activity.

Spasmolytic Activity. (a) A modification of Janssen's method was used.[13] Potency was expressed as the dose that reduced the 5-hr fecal pellet count in mice by 50% as compared to a control group (ED_{50}). (b) Inhibition of charcoal meal transit in rats[14] was used to study **9** and atropine. The per cent of small intestine traversed by the "head" of the meal was calculated for each rat.

Anticholinergic Effects.—The method of Pulewka as modified by Ing, *et al.*,[15] was used to quantitate mydriatic activity. Groups of five to ten mice were used and pupil diameter was measured in arbitrary units at 15–30-min intervals for about 5 hr. Potency was expressed as $ED_{\Delta 6}$, the dose that increased pupil diameter by 6 units. Antisalivary activity was studied in some of the compounds, particularly those with mydriatic activity, by using all-or-none blockade of furtrethonium iodide induced salivation in mice. The ED_{50} was the dose that protected 50% of the mice.

Results

The pharmacological results are shown in Tables IV and V. The hydracrylate derivatives showed effects qualitatively similar to those of atropine. There was no indication that *para* substitution reduced mydriatic on antisalivary effects without a corresponding decrease in spasmolytic potency. The substituted compounds differed from atropine mainly in potency. The halo-substituted compounds **17** and **18** were slightly more potent, while **19** and **20** were about one-tenth and one-fourth as potent, respectively. Additionally, the halo-substituted compounds had a more prolonged mydriatic effect than atropine (see Figures 1 and 2).

In marked contrast to atropine and the hydracrylate derivatives, the acrylates were characterized by a lack of anticholinergic effect as measured by pupillary changes. Also antisalivary activity, tested on **9**, was reduced more than 100-fold compared to the hydracrylate parent compound, atropine. Despite this lack of anticholinergic effect, all of the compounds had some degree of spasmolytic activity, though none were as potent as atropine. Even more important, however, is the virtually complete separation of antisalivary and mydriatic properties from spasmolytic properties in the acrylate series, a separation that has not been achieved with atropine or its analogs.

Of the 4-substituted acrylates, the chloro compound was the most potent, followed by the *t*-butyl and bromo compounds which were almost equipotent. Of the chloroacrylates, the 4-chloro derivative was the most potent, followed by the 3-chloro-2-chloro, and 2,6-dichloro analogs in that order.

TABLE IV
LETHAL, SPASMOLYTIC, AND ANTICHOLINERGIC EFFECTS IN MICE

Compd (free base)	Dose, mg/kg *po*: Mouse MLD	Fecal pellet ED_{50}	Mydriasis $ED_{\Delta 6}$	Antisialogog ED_{50}
9	200	18.2	None	>40
10	135	42.4	*a*	*b*
11	512	76.6	*a*	*b*
12	545	>91.0	312[c]	*b*
13	384	43.0	None	*b*
14	200	54.0	*a*	*b*
15	128	37.3	None	*b*
16	256	>40.5	None	*b*
17	512	1.0	0.92	0.44
18	1024	1.3	0.58	0.33
19	1024	22.4	14.0	3.6
20	1024	10.2	4.4	2.6
Atropine	620	2.5	0.88	0.59
Apoatropine	300	28.6	119.0	37.6

[a] Only at lethal doses. [b] Not tested. [c] Slight mydriasis.

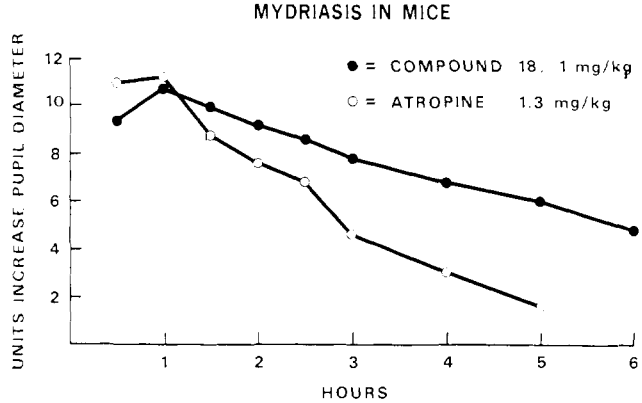


Figure 1.

(13) P. A. J. Janssen, A. H. Jageneau, and J. Huyens, *J. Med. Pharm. Chem.*, 1, 299 (1959).
(14) D. I. Macht and J. Barba-Gose, *J. Am. Pharm. Assoc.*, 20, 558 (1931).
(15) H. R. Ing, G. S. Dawes, and I. Wajda, *J. Pharmacol. Exp. Ther.*, 85, 85 (1945).

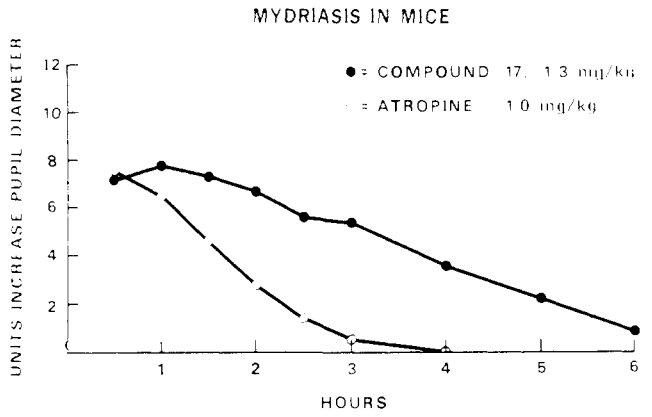


Figure 2.

The 4-halo-substituted compounds **9** and **13** had the largest separation between spasmolytic and lethal effects; **9** was also the most potent and was tested further in comparison to atropine. Compound **9** was not mydriatic in mice and rats, while atropine had a potent effect at doses of 1 mg/kg or less. The antisialogogic activity of **9** was weak in mice, less than $^1/_{100}$th that of atropine. Compound **9** was about one-seventh as potent as atropine in the fecal pellet test. In the charcoal meal test (see Table V), the effects of the two agents were quite different. Atropine produced a maximum of about 50% inhibition at 200 and 400 mg/kg, while **9** produced inhibition ranging from 42 to 94% at doses of 94–185 mg/kg.

Von Oettingen[16] pointed out that the parasympatholytic action of atropine and its analogs was closely connected with the existence of a free alcoholic OH group on the β carbon. The observed virtual abolishment of mydriatic and antisalivary activity among the acrylate type compounds, the main qualitative difference between them and the hydracrylates, would tend to support this idea. The qualitative differences are particularly striking between the acrylates **9**, **13**, and **14** on one hand and the hydracrylates **17–19** on the other.

The acrylates appear to represent a potentially useful class of drugs because they have spasmolytic properties but are nonmydriatic, and thus may not have the side-effect potential of anticholinergic spasmolytics.

TABLE V

INHIBITION OF CHARCOAL MEAL TRANSIT IN RATS

Compd 9		Atropine	
Dose, mg/kg po	% inhib of small intestinal transit	Dose, mg/kg po	% inhib of small intestinal transit
185	93	400	51
148	64	200	52
118	46	100	38
94	42	25	32
		10	10

Acknowledgments.—We are indebted to Miss Margaret Carroll and her staff for microanalysis, to Mr. Robert North for technical assistance, and to Dr. L. C. Greene for encouragement.

(16) W. F. Von Oettingen, "Therapeutic Agents of Pyrrole and Pyridine Group," Edwards, Ann Arbor, Mich., 1936, pp 141–168.

Arundo donax L. (*Graminae*). Phytochemical and Pharmacological Evaluation

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Five indole-3-alkylamine bases, *viz.*, N,N-dimethyltryptamine, 5-methoxy-N-methyltryptamine, bufotenine, dehydrobufotenine, and bufotenidine, were isolated from the rhizomes of *Arundo donax* L. This is the first reported occurrence of bufotenidine and dehydrobufotenine in a plant species. A defatted ethanolic extract of the rhizomes produced hypotensive and antispasmodic effects against histamine-, serotonin-, and acetylcholine-induced spasms. Bufotenidine showed three main pharmacological actions, *viz.*, antiacetylcholine effect which appears to be more specific against skeletal muscle than against muscarinic sites, histamine release, and uterine stimulant. None of these actions of this compound had been reported previously.

Arundo donax L. (*Graminae*), a tall, stout, perennial shrub, often woody below, is widely distributed in India. A decoction of its rhizomes has been used in the Ayurvedic system of medicine[1] as an emollient and diuretic and is said to stimulate menstrual discharge and to diminish the secretion of milk.

From the leaves of this shrub, Madinaveitia previously reported[2] the isolation of three indolic bases, *viz.*, donaxarine, $C_{13}H_{16}N_2O_2$, mp 217°, gramine, and an amorphous phenolic base. Apart from a positive pine splinter reaction and the fact that it cooccurs with gramine little evidence is available regarding the nature of donaxarine. The incomplete characterization of donaxarine and of the amorphous phenolic base by Madinaveitia, and the reported uses of the rhizomes in the Ayurvedic system of medicine prompted us to reinvestigate the basic constituents of this species.

We have previously reported[3] the isolation of five indole-3-alkylamines, *viz.*, N,N-dimethyltryptamine, 5-methoxy-N-methyltryptamine, bufotenine, gramine,

(1) R. N. Chopra, S. L. Nayar, and I. C. Chopra, "Glossary of Indian Medicinal Plants," C.S.I.R., New Delhi, 1956, p 27.

(2) J. Madinaveitia, *J. Chem. Soc.*, 1927 (1937).

(3) S. K. Dutta and S. Ghosal, *Chem. Ind.* (London), 2046 (1967).