Bioavailability, Pharmacokinetics, and Analgesic Activity of Ketamine in Humans

J. A. CLEMENTS *x, **W. S. NIMMO** ‡, **and I. S. GRANT** ‡§

Received May 14, 1981, from the *Heriot-Watt University, Department of Pharmacy, Edinburgh, EH1 2JH, Scotland, and the ‡Departments of Anaesthesia, Western Infirmary, Glasgow, G11 6NT, Scotland. Accepted for publication August 26, 1981. §Present address: Department of Anaesthesia, Ninewells Hospital, Dundee, Scotland.

Abstract □ The pharmacokinetics of ketamine in analgesic doses after intravenous, intramuscular, and oral administration was investigated in healthy volunteers. Plasma ketamine concentration–time curves were fitted by a two-compartment open model with a terminal half-life of 186 min. Absorption after intramuscular injection was rapid and the bioavailability was 93%. However, only 17% of an oral dose was absorbed because of extensive first-pass metabolism. Simultaneous measurements of the elevation of pain threshold in an ischemic exercise test showed a marked effect for 15–60 min after intramuscular injection, but little or no effect after the oral solution. Pain threshold elevation occurred at plasma ketamine concentrations above 160 ng/ml.

Keyphrases □ Ketamine—bioavailability, pharmacokinetics, and analgesic activity in humans, intravenous, intramuscular, and oral administration compared □ Pharmacokinetics—ketamine, intravenous, intramuscular, and oral dosage forms compared □ Anesthetics—ketamine, bioavailability, pharmacokinetics, and analgesic activity in humans

Ketamine [2-*o*-chlorophenyl-2-(methylamino)cyclohexanone] is an anesthetic induction agent which produces sleep rapidly after intravenous injection of 1–2 mg/kg (1). It may also be given by intramuscular injection (6–10 mg/kg) and this route is used extensively in children. The oral route has not been used, although a self-administration of 300 mg and loss of consciousness has been reported (2).

Wieber *et al.* (3) reported the pharmacokinetics of intravenous ketamine (2.5 mg/kg) in five patients to be in accordance with a two-compartment model with a mean terminal half-life of 2.52 hr. Idvall *et al.* (4) found the mean half-life in 31 patients to be 79 min after an intravenous infusion.

In lower doses, ketamine also has analgesic properties (5, 6) and has been used in post-operative pain relief (7–9), but the pharmacokinetics have not been reported.

This paper reports the pharmacokinetics of ketamine in healthy volunteers who received analgesic doses by intravenous and intramuscular injection and as an oral solution. Simultaneous measurements were made of the elevation of the pain threshold in an ischemic exercise test (10).

EXPERIMENTAL

Procedure—In the first study, ketamine hydrochloride[1] was administered by intravenous injection (0.25 or 0.125 mg of base/kg body weight) on separate occasions to five healthy, fasting adult volunteers [age: 33.8 ± 1.4 (*SE*) years; weight: 74.8 ± 2.1 kg]. On a third occasion, an injection of normal saline was given.

In the second study, normal saline or ketamine (0.5 mg/kg) was given to six healthy, fasting adult volunteers [age: 31.8 ± 2.0 (*SE*) years; weight: 70.7 ± 4.4 kg] by intramuscular injection or as an oral solution on separate occasions. On each occasion, the subject drank 50 ml of orange juice with or without ketamine in solution and simultaneously received an intramuscular injection of ketamine or normal saline into the triceps muscle of the dominant arm.

Each study was a crossover design, the order of administration was randomized, and the subject and the person recording pain scores were not aware of the nature of the administered solution. Samples of venous blood (8 ml) were removed from the dominant arm at 0 (blank), 3, 5, 10, 15, 20, 30, and 45 min and at 1, 2, 4, and 7 hr.

Pain Measurements—The method was a modification of the ischemic exercise test of Harrison and Bigelow (10) and was described previously (11). The test was carried out during a 30-min control period before, and at 0, 5, 10, 15, 20, 30, 40, 50, and 60 min (first study) or at 0, 15, 30, 45, 60, 75, 90, and 120 min (second study) after administration of ketamine or normal saline.

Elevation of pain threshold was indicated by a reduction of the "pain score" or an increase in the time to reach intolerable pain, or both, when compared with corresponding values in the subject on the same day during the control period.

Analysis of Blood Samples—Immediately after collection in heparinized tubes, plasma was separated and stored at −20° until as-

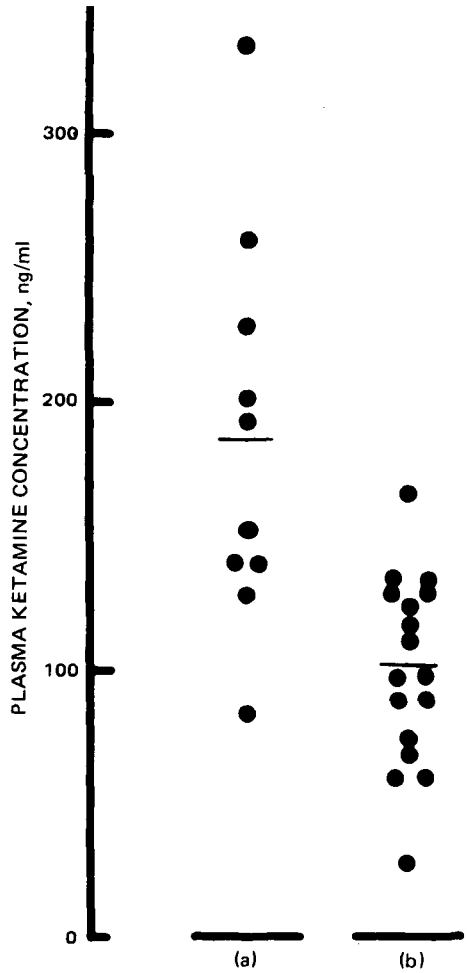

Figure 1—*Distribution of plasma ketamine concentration (ng/ml) that corresponds to pain scores after 75 to 105-sec ischemic exercise of (a) "none" or "mild" or (b) "moderate" or "severe," after intramuscular ketamine (0.5 mg/kg) in six subjects.*

[1] Ketalar, Parke-Davis & Co., Pontypool, U.K.

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Table I—Absorption Rate Constants (K_a, min^{-1}) and Bioavailability (F) of Ketamine, 0.5 mg/kg, Given by Intramuscular Injection or as an Oral Solution

Subject	Intramuscular Injection[a]			Oral Solution		
	K_a'	K_a''	F_{area}	F_{area}	F (Eq. 1)	F (Eq. 2)
1	0.040	0.038	0.965	0.145	0.032	0.160
2	0.054	0.043	0.923	0.163	0.204	0.190
3	0.412	—	—	—	—	0.155
4	0.285	0.130	0.972	0.112	0.092	0.115
5	0.069	—	—	—	—	0.309
6	0.142	0.146	0.859	0.245	0.158	0.239
Mean	—	—	0.930	0.166	—	0.195
SE	—	—	0.026	0.028	—	0.028

[a] K_a' from nonlinear regression. K_a'' from method of Loo-Riegelman (22).

sayed. Plasma samples were analyzed in duplicate or triplicate for ketamine and norketamine (metabolite 1) as their heptafluorobutyryl derivatives on a gas chromatograph with electron-capture detection (12–14). Dehydronorketamine (metabolite 2) consistently gave two peaks on the chromatogram; this was observed previously by White *et al.* (15).

Pharmacokinetic Analysis—Plasma ketamine concentrations were fitted to a two-compartment model by nonlinear regression with a simplex algorithm (16, 17); individual data points were weighted as recommended by Ottaway (18).

Preliminary estimates of the apparent volume of the central compartment, the absorption rate constant (second study), and transfer microconstants were obtained using an analog computer. Goodness of fit criteria used were the run test and the number test on the signs of the residuals (19) and a test statistic for serial correlation between residuals (20). Both of these criteria indicated a satisfactory fit in all cases.

The bioavailability (F_{area}) was calculated from the ratio of the trapezoidal area (with correction for the area beyond the last data point and adjustment for dose) after intramuscular or oral administration to that after intravenous injection in the same subject. Apparent distribution volumes of the central compartment (V_1), at steady-state ($V_{d_{ss}}$), and during the terminal phase (V_{d_β}) and total body clearance values (TBC) (21), were not corrected for bioavailability. Estimates of the absorption rate constant were also obtained by the method of Loo and Riegelman (22).

The fraction of the dose lost by first-pass metabolism (F) was calculated from:

$$F = 1 - \frac{TBC}{Q_1} \qquad \text{(Eq. 1)}$$

where TBC is the clearance value for ketamine after intravenous injection and Q_1, the hepatic blood flow, was taken as 1.53 liters/min (23), and from:

$$F = \frac{Q_1}{Q_1 + X_0/(AUC)_{oral}} \qquad \text{(Eq. 2)}$$

where $(AUC)_{oral}$ is the area under the plasma ketamine concentration–time curve after oral administration of the dose X_0 (21).

The Student t test was used in tests of statistical significance.

RESULTS

Pharmacokinetics—Immediately after intravenous injection, plasma ketamine concentrations fell rapidly, and the data were fitted by a two-compartment open model with a mean terminal half-life of 186 ± 10 min. The concentration y (ng/ml) at time t(min) after injection was given by:

$$y = 82\exp(-0.044t) + 22\exp(-0.0039t)$$

after a 0.125 mg/kg dose (Eq. 3)

and by:

$$y = 108\exp(-0.039t) + 40\exp(-0.0038t)$$

after a 0.25 mg/kg dose (Eq. 4)

There were no significant differences in the values of α, β, apparent distribution volumes, or clearance for the two doses.

Ketamine was rapidly absorbed after intramuscular injection with apparent absorption half-times of 2–17 min. The estimated interval between the injection and the appearance of ketamine in the plasma (lag time) was less than 4 min and the bioavailability was 93% (Table I). Apparent peak concentrations (C_{max}) of between 100 and 425 ng/ml occurred at 5–30 min (t_{max}) after injection. Absorption rate constants calculated by the Loo–Riegelman method agreed well with those from nonlinear regression, except in one subject in whom absorption was very rapid. The mean (±SE) terminal plasma half-life (155 ± 12 min) did not differ significantly from that after intravenous injection (186 ± 10 min) and no difference was observed in the clearance values (23.2 and 19.1 ml/min/kg, respectively) (Table II).

After oral administration, ketamine absorption was incomplete, with only 16.6% of the dose reaching the systemic circulation. The lag time was between 4 and 13 min (mean 8.0 min). The mean apparent peak concentration of 44 ng/ml (range 15–80 ng/ml) was much lower than the value (243 ng/ml) after intramuscular injection (Table II). The fractions of the oral dose available to the systemic circulation, as calculated from Eq. 2, were in close agreement with observed values; however, the fractions predicted from clearance values after intravenous injection (Eq. 1) agreed well in only two of the four subjects (Table I).

Norketamine was found in measurable concentrations after each route of administration. After intravenous injections of 0.125 and 0.25 mg/kg, apparent peak concentrations of 15–30 ng/ml and 20–60 ng/ml, respectively, occurred at 15–60 min. Areas under the plasma norketamine concentration–time curves (corrected for dose) did not differ significantly. Although the mean peak norketamine concentration after oral admin-

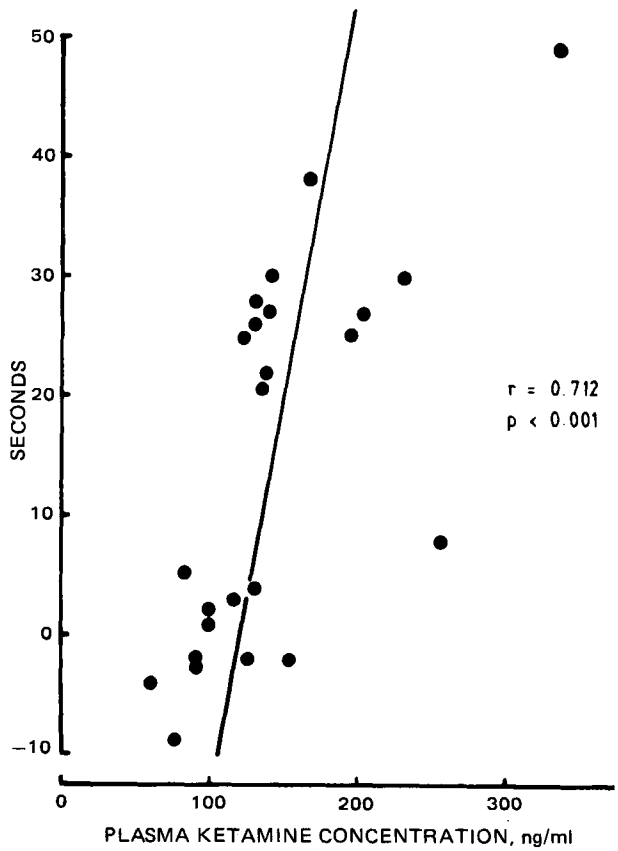

Figure 2—*Increase in time of ischemic exercise to intolerable pain (sec)* versus *plasma ketamine concentrations (ng/ml) after intramuscular injection of ketamine (0.5 mg/kg) in six subjects.*

Table II—Pharmacokinetic Values (Mean ± *SE*) for Ketamine and Norketamine in Fasting Volunteers after Intravenous Injection, Intramuscular Injection, or Oral Administration of Ketamine [a]

Pharmacokinetic Value	Administration Route, dose: Intravenous Injection, 0.25 mg/kg	Intramuscular Injection, 0.5 mg/kg	Oral Solution, 0.5 mg/kg
	Ketamine		
C_{max}, ng/ml	—	243 (49)	44 (10)
t_{max}, min	—	22 (4)	30 (5)
Half-life ($t_{1/2\beta}$), min	186 (8)	155 (12)	174 (50)
AUC[b], min ng/ml	27.5 (1.2)	23.6 (2.2)	4.8 (0.8)
TBC[c], ml/min kg	19.1 (1.1)	23.2 (2.7)	—
	Norketamine		
C_{max}, ng/ml	40 (6)	92 (10)	200 (44)
t_{max}, min	63 (23)	78 (14)	60 (13)
AUC, min ng/ml	35.4 (3.8)	31.3 (3.8)	36.7 (3.9)

[a] $N = 6$. [b] *AUC*, area under plasma concentration time curve, corrected to an administered dose of 0.5 mg/kg. [c] *TBC*, clearance value, not corrected for bioavailability.

istration was higher than after intramuscular injection, the areas were similar and neither differed significantly from that after intravenous injection (Table II).

Pain Measurements—In the control period, before administration of ketamine or normal saline, severe pain was observed after 75–105 sec of exercise and was reproducible in each individual on each occasion. The pain became intolerable after a further 7 sec (range 1–13 sec). The pain threshold was considered to have been raised when the pain was graded as "none" or "mild" at these times, or when the time to reach intolerable pain was significantly prolonged, or both.

After intravenous injection of ketamine, the pain threshold elevation lasted for less than 10 min after 0.25 mg/kg and less than 5 min after 0.125 mg/kg (14). At 15 and 30 min after intramuscular injection of ketamine, the period of ischemic exercise before pain became intolerable was significantly prolonged, by 24 and 21 sec, respectively. At later times, and also after injection of normal saline, the period was not prolonged (11).

Elevation of pain threshold after intramuscular injection occurred in all individuals for up to 1 hr; the corresponding plasma ketamine concentrations were between 85 and 330 ng/ml. Concentrations that corresponded to a pain score of "none" or "mild" after 75–105 sec of ischemic exercise were significantly higher (186 ± 23 ng/ml) than those when pain scores were "moderate" or "severe" (101 ± 8 ng/ml) (Fig. 1). There was a significant correlation between the plasma ketamine concentrations and the increase in time taken to reach intolerable pain (Fig. 2) in the hour after injection, but no significant correlation was found for norketamine concentrations.

After oral administration, pain thresholds were not markedly elevated, and subjects experienced moderate or severe pain after 75–105 sec of ischemic exercise. The mean increase in exercise time before intolerable pain was reached was not significant except at 30 min after administration when the increase (9 sec) reached significance ($0.05 > p > 0.025$). Plasma ketamine concentrations were between 17 and 65 ng/ml. Norketamine concentrations were higher, in the range 80–390 ng/ml. No significant correlations were observed between plasma ketamine or plasma norketamine concentrations and the increase in time to reach intolerable pain.

DISCUSSION

The pharmacokinetics of intravenous ketamine in the analgesic doses used in this study are similar to those previously reported for anesthetic doses (3). Plasma concentration–time data were adequately fitted by a two-compartment open model, and apparent distribution volumes, terminal plasma half-lives, and clearance values after analgesic doses (0.125 or 0.25 mg/kg) in volunteers did not differ significantly from those reported for anesthetic doses (2.5 mg/kg) in patients (14). Mean terminal plasma half-lives after anesthetic and analgesic doses were 151 and 186 min, respectively. Both times are much longer than the value (79 min) reported for patients at the end of an intravenous infusion (4). This difference is attributed to the relatively short sampling period (2–2.5 hr) used in the latter study, since early termination of sample leads to underestimation of the half-life (24). Analysis of data for this period after intravenous injection of ketamine gave an apparent half-life of 105 min.

The low plasma ketamine concentrations after oral administration could have been due to incomplete absorption from the GI tract or to extensive metabolism during the first-pass through the liver. The relatively high concentrations of the metabolite norketamine suggest that liver metabolism is largely responsible. Where the liver is the sole site of metabolism, the area under the curve of concentration of metabolite *versus* time is independent of route of administration (25). Since the area under the norketamine concentration–time curves after oral administration was similar to that after intravenous injection (after correction for dose), the low plasma ketamine concentrations can be attributed solely to the extensive first-pass metabolism. Also, the fraction of the oral dose reaching the systemic circulation, as calculated from Eq. 2 on the assumption that absorption from the gut lumen was complete, was in good agreement with F_{area}, the fraction calculated from area analysis.

Estimation of the fraction of an oral dose reaching system circulation from areas after intravenous injection, using Eq. 1, gave good agreement in two subjects but underestimated the values in two.

Since elevation of pain threshold was previously reported to be associated with plasma ketamine concentrations above 100–150 ng/ml (11, 14), the absence of any marked effect after oral administration may be explained by the low concentrations of ketamine as these did not exceed 80 ng/ml. Norketamine has been shown to have pharmacological activity, including analgesic properties, in the rat (15) but its effects in humans are not known. As high norketamine concentrations, up to 390 ng/ml, were found in some subjects after oral administration of ketamine, it is possible that this metabolite, either alone or in combination with ketamine, was responsible for the small increase in time taken to reach intolerable pain during ischemic exercise. However, no correlation was observed between the increase in time to reach intolerable pain and plasma norketamine concentration. The activity of other metabolites formed by hydroxylation of the cyclohexanone ring (Metabolites 3 and 4) is not known and these are not measured in the assay. In view of the extensive first-pass metabolism, oral administration of ketamine in a dose of 0.5 mg/kg is not satisfactory for producing analgesia.

After intramuscular injection, ketamine was rapidly and almost completely absorbed, and the fall in the terminal plasma concentrations represented the elimination phase, since the half-life did not differ from that observed after intravenous injection.

Intramuscular injection of ketamine produced a marked elevation of pain threshold for between 15 and 60 min. Using the criterion of a pain score of "none" or "mild," after 75 to 105 sec of ischemic exercise or an increase of 20 sec or more in the time to intolerable pain, it was found that elevation of pain occurred consistently at plasma ketamine concentrations exceeding 160 ng/ml, but not at concentrations below 80 ng/ml (Fig. 1). These data make it possible to design dosage regimens and may increase the usefulness of ketamine as an analgesic agent.

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Synthesis, Hydrolytic Reactivity, and Anticancer Evaluation of *N*- and *O*-Triorganosilylated Compounds as New Types of Potential Prodrugs

FANG-TING CHIU, YOUNG HWAN CHANG, GÜNAY ÖZKAN, GERALD ZON ×, KENNETH C. FICHTER *, and LAWRENCE R. PHILLIPS ‡

Received April 24, 1981, from the *Department of Chemistry, The Catholic University of America, Washington, DC 20064*, the **Mid-Atlantic Research Institute, Bethesda, MD 20014*, and the ‡*Bureau of Biologics, Food and Drug Administration, Bethesda, MD 20205.* Accepted for publication August 6, 1981.

Abstract □ *N*- and *O*-Triorganosilylated compounds related to various anticancer agents were synthesized for evaluation as potential anticancer prodrugs. ^{1}H-NMR and UV kinetic measurements of hydrolytic desilylation were used to correlate relative rates of structural unmasking with steric bulk about the silicon reaction center. The *tert*-butyldimethylsilyl ester of chlorambucil and a number of *O*-triorganosilylated carbamate derivatives of nor-nitrogen mustard showed significant activity against P-388 lymphocytic leukemia in mice.

Keyphrases □ Prodrugs—*N*- and *O*-triorganosilylated compounds, synthesis, potential anticancer prodrug □ Anticancer agents—synthesis of *N*- and *O*-triorganosilylated compounds, potential anticancer prodrugs □ Triorganosilylated compounds—synthesis and evaluation of potential anticancer prodrugs

In an earlier investigation of potential anticancer prodrugs (1), it was found that *O*-aryl-*N*,*N*-bis(2-chloroethyl)phosphorodiamidates are resistant toward chemical activation involving P-OAr hydrolysis and failed to provide evidence for *in vivo* formation of phosphoramide mustards, which are usually cytotoxic and may exhibit anticancer activity (2). The hydrolytic lability (3) of Si—N and Si—O bonds suggested that strategically triorganosilylated derivatives of known oncostatic agents might constitute a class of compounds which are, for kinetic reasons, more suitable candidates for anticancer prodrugs. The possibility of controlling drug unmasking rates (desilylation) by manipulating the nature of the silicon reaction center represents an interesting feature of these hypothetical compounds. The expected hydrolysis byproducts, namely triorganosilanols and disiloxanes, are generally nontoxic (4). Derivatization with a triorganosilyl group increases lipophilicity; consequently, triorganosilyl prodrugs might eventually prove to be useful against central nervous system cancers, which apparently require somewhat more lipophilic chemotherapeutic agents for effective penetration of the blood–brain barrier (5).

In view of the widespread interest in the design of anticancer prodrugs (6, 7) and the development of organosilicon compounds as medicinal agents (8), the aforementioned proposal is unique in that it encompasses both of these growing research areas. This report is the first of a series of exploratory investigations of hydrolytically labile *N*- and *O*-triorganosilyl prodrugs having potential anticancer activity. These studies include the synthesis of several new classes of nitrogen mustards, measurement of hydrolytic desilylation rates by a combination of ^{1}H-NMR and UV methods, examination of the hydrolysis mechanisms by Hammett-type kinetic studies and ^{18}O-labeling, and the comparison of screening results obtained with experimental cancers in mice.

EXPERIMENTAL

NMR refers to ^{1}H-NMR at 60 MHz, except as noted; chemical shifts refer to deuterochloroform and are relative to internal tetramethylsilane, unless specified otherwise. ^{31}P-NMR spectra were recorded at 40.25 MHz using a $\pi/2$ pulse (13 μsec) and a 2-sec repetition time. All organosilicon starting materials were commercially available and were checked for purity by NMR; if necessary, further purification was achieved by either conventional distillation or recrystallization. All handling and reactions of organosilicon compounds were performed under an atmosphere of dry nitrogen; all reagents and solvents were anhydrous. Satisfactory elemental analyses were not always possible, due to hydrolytic reactivity. However, each product was reliably characterized by NMR as well as IR (9–11) and/or mass spectroscopy. In all cases, NMR signal integrations established that product purity was >90%. Electron-impact mass spectra were scanned from samples introduced *via* a solids' direct probe inlet. The probe, when loaded with a sample and properly positioned with respect to the ion source, was heated at 100°/min from ambient temperature to a final temperature of 320°. The ion source temperature was 180°, the ionizing potential was 70 eV, and the ionizing current was 50 μA. Analytical thin-layer chromatography (TLC) employed 2.5 × 10-cm plates coated with a 250-μm layer of silica gel containing a fluorescent indicator; component visualization was achieved with iodine vapor and/or a short wavelength UV lamp. Column chromatography utilized 60–200 mesh silica gel, which was dried by heating at 150° for 24 hr and then cooling to room temperature under nitrogen.

All compounds having a bis(2-chloroethyl)amino functionality are potentially toxic and/or mutagenic and should be handled with extreme care.

***O,O*-Dimethyl-*N,N*-bis(2-chloroethyl)phosphoramidate (III)** —Lithium methoxide was prepared fresh by slowly adding a benzene solution (10 ml) of methanol (6.5 ml) to a mixture of benzene (10 ml) and sliced lithium wire (15 cm, 6.11 mmoles/cm) at 25°. After an additional 3 hr of stirring, a solution of I (12) (10.4 g, 40 mmoles) in benzene (40 ml)

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